MASTER OF SCIENCE

The Impact of Genetic Testing in Women with a Diagnosis and Family History of Breast Cancer
A Qualitative Investigation of Patient Experience

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The Impact of Genetic Testing in Women with a Diagnosis and Family History of Breast Cancer: A Qualitative Investigation of Patient Experience

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1. ACKNOWLEDGEMENTS

Dedication: This project is dedicated to the women who participated in this research and my dear friend, Zoi McEachan, who was diagnosed with breast cancer shortly after my research proposal was accepted by the University of Dundee. Sadly Zoi did not survive to see this finished thesis. My thoughts of Zoi and women whose lives I have touched through this research motivated me to complete this work.

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2. DECLARATIONS

Pauline Armory is the author of this thesis.

The work of which this thesis is a record has been carried out by Pauline Armory.

All references cited have been consulted by Pauline Armory.

This work has not been previously accepted for a higher degree.

Signature: Date:

Pauline E. Armory

The conditions of the relevant Ordinance and Regulations have been fulfilled.

Signature: Date:

Dr Jonathan Berg, Supervisor

3. ABSTRACT

Personalised Medicine has the potential to impact cancer prevention, diagnosis, treatment and prognosis. Today efficient, affordable and available early BRCA1/2 screening techniques are now feasible and can provide results to inform treatment. However BRCA1/2 testing, undertaken close to cancer diagnosis, can represent an added burden for patients during a highly stressful time. This study aimed to investigate BRCA1/2 gene testing experiences and the impact these have on treatment decisions in women with hereditary breast cancer.

In-depth interviews with 17 women explored genetic knowledge, test timing and impact of results on treatment choices. Secondary data analysis has been conducted using 5 interview recordings, obtained from a previous study. Inductive analysis, based on Grounded Theory, has been assisted by the Framework Approach. Comparative methods have produced rich qualitative data that illustrates diverse genetic testing experiences, opinions and treatment decisions.

Personalised treatment to maximise survival was identified as a significant factor in patient support and uptake of early BRCA1/2 testing. Participants propose that '*it makes sense*' to obtain early genetic information. Genetic status can be used to inform and assist '*tailored treatment*' decisions, including risk-reducing interventions.

Clinical progression towards early genetic testing to inform treatment for newly diagnosed hereditary breast cancer appears to be acceptable and feasible. The offer of a genetic test at the time of diagnosis is new in the field of cancer genetics, we need to optimise the way in which this technique is used to provide health advantage for patients and clinicians. Future study should focus on the acceptability of the integration of personalised medicine techniques, within current clinical pathways.

List of Abbreviations

AI: Aromatase Inhibitors

BCT: Breast Conserving Therapy

BRCA: Breast Cancer (Gene)

BMSc: Bachelor of Medical Science

CAQDAS: Computer Assisted Qualitative Analysis

CBC: Contralateral Breast Cancer

CRF: Clinical Research Facility

CRRM: Contralateral Risk Reducing Mastectomy

DNA: Deoxyribonucleic Acid

FDA: Food and Drug Administration

FHBCC: Family History Breast Cancer Clinic

HBOC: Hereditary Breast and Ovarian Cancer

HER2: Human Epidermal Growth Factor Receptor 2

HD: Huntington's Disease

ICF: Informed Consent Form

GCP: (International Conference on Harmonisation) Good Clinical Practice guidelines for clinical trials

LHRH: Luteinising Hormone Releasing Hormone

MDT: Multi-Disciplinary Team

MHRA: Medicines and Healthcare Products Regulatory Agency

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

PARP: Poly ADP-Ribose Polymerase

PI: Principal Investigator

PIS: Participant Information Sheet

RRBSO: Risk Reducing Bilateral Salpingo-Oophorectomy

SIGN: Scottish Intercollegiate Guidelines Network

SERM: Selected Oestrogen Receptor Modulators

TASC: Tayside Medical Science Centre

UK: United Kingdom

4. INTRODUCTION

Hereditary Breast Cancer & the BRCA Genes

Breast cancer is the most common female cancer (Ferlay et al., 2013). Excluding age, family history is one of the most significant factors in determining risk (Antoniou and Easton, 2006). In a general population 1 in 450 people will carry a BRCA1/2 mutation (CGHFBG, 2001); correspondingly between 5 and 10% of breast cancers are BRCA1/2 related (Claus et al., 1996). Typically these tumours are more invasive and respond less predictably than sporadic cancers, furthermore they are associated with a high recurrence risk (Shuen and Foulkes, 2011).

BRCA mutations are the most common cause of hereditary breast cancer (Miki et al., 1994, Wooster et al., 1995) and within a hereditary population women who present with breast cancer and an extensive family history will most probably have a BRCA mutation (Eccles and Pichert, 2005). For these women, the option for early genetic testing is now clinically feasible with results available within 3 weeks to inform treatment (Wevers et al., 2014).

The current research agenda requires evidence to improve hereditary cancer outcomes (Eccles et al., 2013, NICE, 2013b). Early genetic testing, carried out close to diagnosis, can bring significant benefit; informing treatment and risk-reduction decisions to improve patient outcomes (Wevers et al., 2012a, Metcalfe et al., 2014). Closely related to this, a reduced threshold for predictive BRCA testing has been provided in the 2013 national clinical guidelines (SIGN, 2013, NICE, 2013b), however there is no current guidance for early testing.

BRCA1/2 testing undertaken close to the time of a cancer diagnosis can represent an added burden for patients during a highly stressful time (Wevers et al., 2012b). At the outset of this project, little was known of the hereditary breast cancer genetic testing patient experience. Correspondingly this research study was developed, primarily to explore opinions about genetic testing.

Study Overview

This qualitative, in-depth interview study aimed to investigate BRCA1/2 gene testing experiences and the impact these have on treatment decisions in women with hereditary breast cancer. Data has been obtained to represent the experience and opinions of 17 patients under the care of NHS Tayside Clinical Genetics Department. Grounded Theory has formed the basis for inductive analysis. Comparative techniques have been adopted to produce rich qualitative data that illustrates diverse genetic testing experiences, opinions and treatment decisions.

Research Interest & Study Relevance

My interest in hereditary breast cancer was captured in 2009 whilst working as a research nurse for Breast Cancer Campaign Tissue Bank. At this time I observed a situation that was evolving within the field of Breast Cancer and Clinical Genetics. The availability of new genetic technologies and techniques created the option for providing genetic information, for the highly penetrant BRCA1/2 genes, before starting targeted breast cancer treatment.

At the outset of this project, early genetic testing for women with a hereditary breast cancer diagnosis was rarely undertaken and while early testing remains relatively uncommon in 2015, it is becoming more usual. It is anticipated, that for women with a hereditary breast cancer diagnosis, early testing to inform treatment will become routine practice. Subsequently this research study was conceived, to create understanding and develop theory relating to the patient experience of genetic testing in NHS Tayside.

It is expected that the results of this research will assist Clinical Genetics and the extended Breast Care Team in NHS Tayside to develop evidence-based care for high risk breast cancer patients. The study findings will be presented locally; national dissemination will occur by conference presentation[1] and peer review publication.

Thesis Structure

This report aims firstly, in the literature review chapter, to define relevant theory and to answer questions relating to the main issues that surround early BRCA1/2 gene testing for the hereditary breast cancer patient. Literature detailed throughout has been accessed during the project which spanned 5 years, and commenced in 2010. During this period the hereditary breast cancer and early genetic testing landscape have evolved considerably; furthermore the related clinical and technological advances have resulted in improved patient outcomes. Literature obtained early in the project assisted the development of the research questions and the study aims and objectives.

[1] Abstract accepted for British Association of Cancer Research (Breast Cancer Conference) 2015.

Subsequent literature searches have provided further evidence for the clinical relevance and patient acceptance of early genetic testing. While this evidence has been used within the literature review chapter, to frame the main issues, these theory have not informed the data analysis or thematic development.
However these later theory have been used deductively to corroborate the study findings, correspondingly they are included in the discussion chapter.

The chapters that follow the literature review detail the study aims and objectives, methodology, including limitations, and ethical issues. Additional information to assist the reader has been provided in footnotes and appendices, referenced throughout the report. The study findings chapter uses an abundance of verbatim quotations to illustrate participant opinion. Findings are presented systematically using the 4 main analytic categories that evolved inductively from the data. Each category is reported and begins with a summary of the key findings, thereafter detail is provided using the inductively developed sub-categories. Reference to Figure 12: BRCA Test Topic, Analytic Categories & Sub-Categories (pg 124) is recommended to assist the reader's progress through the study findings chapter.

The discussion chapter presents the findings in accordance with the 5 study objectives, using associated headings. Published theory, including factors that influence patient decisions and opinions, are woven throughout discussion text. In concluding, 5 key questions, relating to the study objectives, have been answered using theory derived from this data analysis.

5. LITERATURE REVIEW

5.1 Why Offer Early Genetic Testing?

Approximately 5-10% of breast cancers are caused by highly penetrant genes (Claus et al., 1996). The biology and response of BRCA-related breast cancer differs from that of sporadic cancers (CGHFBG, 2001). Tumours are often larger, more aggressive and response to conventional treatment less predictable (Shuen and Foulkes, 2011).

The option to offer early genetic testing is today a clinically feasible option with results available within 3 weeks to inform treatment (Wevers et al., 2012b, Trainer et al., 2010b). Personalised BRCA breast cancer treatment and risk-reduction interventions have been used with demonstrable improvements in patient outcomes and survival (Metcalfe et al., 2014, Narod et al., 2013, Cooper et al., 2013).

Social, ethical and clinical debate have not slowed the molecular genetic technological advances that have resulted in efficient and affordable genetic screening techniques for BRCA1 and BRCA2, the results of which can be incorporated into increasingly personalised care (McGowan et al., 2014, Ginsburg and Willard, 2009). Early genetic testing, at the time of diagnosis, to inform and personalise treatment for women with breast cancer and relevant risk factors, such as a strong family history (Meiser et al., 2008) or a triple negative tumour (Robertson et al., 2012), is now a feasible option. However the impacts for the patient group must be considered (Ardern-Jones et al., 2005, Wevers et al., 2012b).

Acceptability of Early Testing

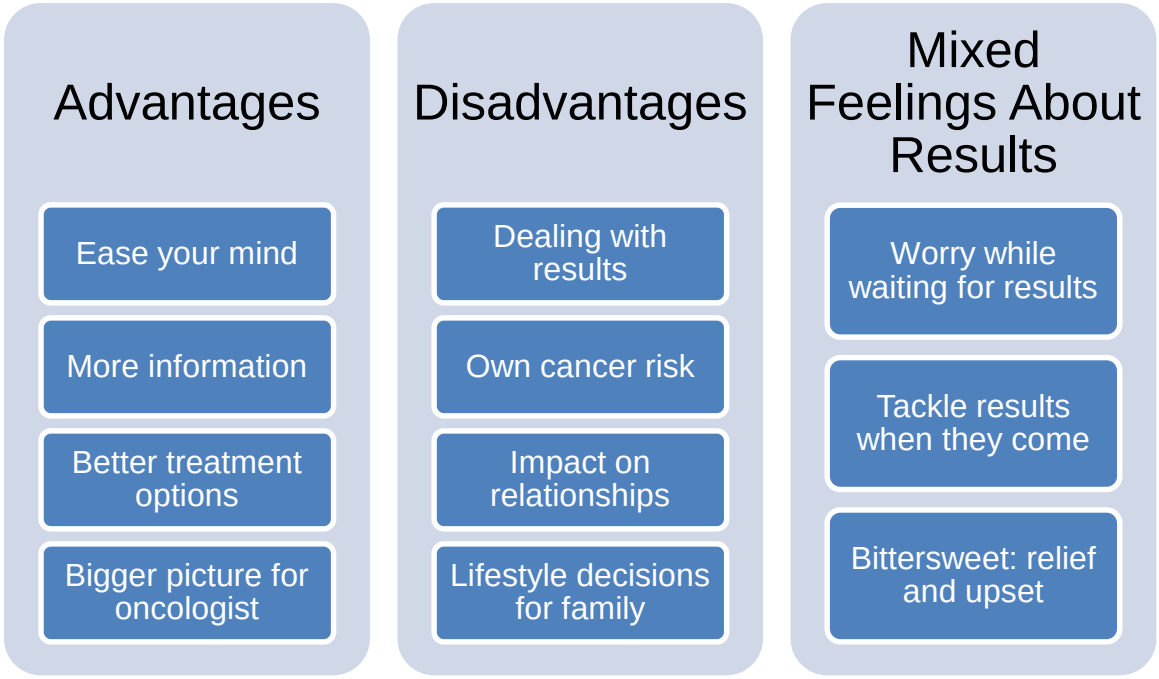
Recent evidence suggests that knowledge of BRCA1/2 gene mutation status at diagnosis can influence surgical and potentially, chemotherapy, radiotherapy and endocrine therapy choices for women with breast cancer (Weitzel, 2003, Haffty, 2002, Schwartz, 2004, Pierce, 2000, Smith and Isaacs, 2011). Current treatment pathways can provide increasingly personalised care for women with a BRCA1/2 mutation, a mutation of uncertain significance or no mutation in the presence of hereditary breast cancer. Thus genetic testing at the time of diagnosis is increasingly being considered as an option for and by these patients (Schwartz, 2005, Francken et al., 2013, Smith and Isaacs, 2011, Euhus and Robinson, 2012). Regardless of this, concerns regarding the impact of genetic testing immediately post-diagnosis remain (Francken et al., 2013, Schwartz et al., 2005).

The option for a BRCA1/2 genetic test, to establish hereditary or genetic nature of their cancer, does not come without significant psychological burden for patients and their families. This is particularly relevant when testing is proposed at or close to cancer diagnosis, an already highly stressful time (Glanz, 1992, Wevers et al., 2011b, Eijzenga, 2014, Bombard et al., 2014). The decision to offer genetic testing at diagnosis is not an easy one.

A study that focused on BRCA status for women with ovarian cancer reported that acceptance of treatment focused early genetic testing is based on the option to receive targeted cancer treatment (Meiser et al., 2012a). Participants conveyed that this benefit outweighed perceived disadvantages. Of significance, the women in a later study (Meiser et al., 2012b) also supported early testing, even if the only

purpose was to obtain genetic information for family benefit, including three participants who had no children. Perceived advantages and disadvantages of treatment focused genetic testing are shown in Figure 1.

Figure 1: Early Genetic Testing Patient Opinions



Source / Adapted from (Meiser et al., 2012a)

Despite concerns, patient and professional acceptance of early genetic testing is high (Burcher et al., 2013, Meiser et al., 2012b, Wevers et al., 2012b). Acceptance is exemplified in the following quote regarding whether patients require time or assistance to consider the option of an early genetic test:

> (there is) “no decision to make” p156 (Meiser et al., 2012a).

A study conducted in Australia concluded that women aged below 50 want to be informed about ‘Treatment-Focused Genetic Testing’ at or around the time of diagnosis, when treatments are being discussed and before a final decision is made.

The primary reason for these women seeking genetic information is to guide initial cancer treatment and future risk management (Meiser et al., 2012b). Similar findings are reported in a Dutch study (Wevers et al., 2012b); women state gaining certainty, about the risk of developing further breast cancer, is the prime reason for undertaking early genetic testing. Associated with this is a desire to choose the most appropriate treatment to reduce future surgeries and cancer treatments.

An earlier publication by Meiser (Meiser et al., 2012a) reported that post-diagnosis vulnerability increased patient acceptance of treatment focused early genetic testing. The possibility of obtaining information that will tailor treatment and improve survival is described as one of the highest priorities. However at the time of diagnosis women may feel overwhelmed by a life-threatening diagnosis and treatment options (Meiser et al., 2012a). A small number of patients chose to withdraw from early genetic testing for this reason (Watts et al., 2012). To ensure that all high risk patients who meet early testing criteria are offered BRCA1/2 testing at a time that suits them Watts (2012) recommends a process that enables patients, who do not wish to proceed before primary cancer treatment, to receive a genetics referral at a later date. Similarly, some women describe not wanting to wait for genetic results before having initial treatment, even when personalised treatment will be available very soon after receiving genetic results. For these women delayed personalised treatment can follow initial cancer treatment (Wevers et al., 2012b).

Information Delivery

The method of delivering genetic test information to patients has been explored in a qualitative study (Meiser et al., 2012b). The majority of participants wanted early

genetic testing to be discussed before cancer management decisions were made and some preferred genetic testing to be discussed at the time of diagnosis. The following dialogue supports the option for integrating genetic testing with treatment planning:

> "at the start, as part of being diagnosed" E105 (Meiser et al., 2012a).

In the study a range of healthcare professionals were proposed to introduce genetic testing, though no clear majority emerged from the more popular choices of surgeon, oncologist or breast care nurse (Meiser et al., 2012b). Face-to-face consultation was the overwhelming preference for information delivery[2]. This direct method allows for spontaneous questioning and a more personalised approach that enables a family member or close friend to support the patient.

A prospective study is currently underway to further explore how to discuss early genetic testing (Watts et al., 2012). The study aims to provide evidence for safe and effective clinical genetics care pathway, for treatment focused genetic testing especially for newly diagnosed younger women.

[2] Supplementary written information was viewed as essential by most participants MEISER, B., GLEESON, M., WATTS, K., PEATE, M., ZILLIACUS, E., BARLOW STEWART, K., SAUNDERS, C., MITCHELL, G. & KIRK, J. 2012b. Getting to the Point: What Women Newly Diagnosed With Breast Cancer Want to Know About Treatment-Focused Genetic Testing. *Oncology nursing forum,* 39**,** E101-E111.. This allows patients to take in the information in their own time and consider questions. Different formats of written information have been proposed, either a leaflet, DVD or website with each containing the same information. Some felt that the DVD or website were not required. Most women were satisfied with a leaflet as a source of supplementary information. Additionally most reported that the leaflet improved their understanding, particularly in relation to the purpose of early genetic testing.

Responses to Early Testing

An early study of expedited genetic assessment proposed that treatment focused testing is indicated for high risk women who would consider risk-reducing mastectomy and oophorectomy (Meiser et al., 2008). More recent studies have established that knowledge of carrier status before primary breast cancer treatment influences treatment choices (Wevers et al., 2012a), and suggest that women with newly diagnosed breast cancer benefit from the knowledge that they carry a BRCA mutation (Metcalfe et al., 2014).

Confirmation of a BRCA1/2 mutation is predictive for establishing contralateral breast cancer risk and is of crucial importance when deciding whether contralateral prophylactic mastectomy is indicated (Rhiem et al., 2012, Graeser et al., 2009). Following rapid genetic testing and counselling Wevers et al (2012 & 2014) report an increasing trend in the uptake of bilateral mastectomies at the time of first surgery (Wevers et al., 2012b, Wevers et al., 2014).

Bilateral mastectomy (Metcalfe et al., 2014) and personalised regimen using targeted adjuvant therapies (EBCTCG, 2011, Cooper et al., 2013, Shuen and Foulkes, 2011) are justified for women identified with a BRCA1/2 mutation. Survival data for women with BRCA1/2 mutation supports the use of early genetic testing to establish status prior to exploiting the unique biology of BRCA-related tumours, with specific chemotherapy (Narod et al., 2013) and new adjuvant agents such as platinum based agents (Byrski et al., 2012) and adjuvant PARP inhibitors (Smith et al., 2014).

Personalised cancer treatments and strategies to stop future cancers are fundamental to the value of early genetic testing for women with a diagnosis and family history of breast cancer.

5.2 Genetic Care: An Overview

A High Risk Population

The number of people with a mutation in either BRCA gene is small however the impact of a genetic fault for the individual, their family and health care is significant (Stratton, 1997, Chappuis et al., 1999). Research has established that approximately 2 in 1,000 people carry a BRCA gene mutation (Antoniou et al., 2002) and it is estimated that 1 in 20 women diagnosed in the UK with breast cancer have a fault in either BRCA1 or BRCA2 (CancerResearchUK, 2012).

These two highly penetrant single gene mutations confer a significant lifetime risk for developing breast cancer (Antoniou et al., 2002). For women carrying a BRCA1 gene mutation the lifetime risk for breast cancer is reported between 65 and 85% and estimates for BRCA2 vary between 40 and 85% (Antoniou et al., 2003). Importantly BRCA1/2 mutation carriers are more likely to develop early onset and bilateral breast cancer (Ford and Easton, 1995, Antoniou et al., 2003, Claus et al., 1996).

Personalising Medicine

The consequences for individuals with BRCA gene mutations have resulted in these genes being the focus of substantial scrutiny and the development of molecular

techniques for identifying mutations. The impact of a mutation in relation to patient outcome and survival is now understood (Nilsson et al., 2014). Current work and clinical guidelines are focusing on developing and providing personalised treatments (Couch et al., 2014, NICE, 2013a).

The concept of personalised medicine[3] has gained increasing global acceptance over the last two decades (Jackson and Chester, 2014, Couch et al., 2014, Daly, 2004). Whilst many governments, health care agencies and the public support a shift towards personalised medicine the accessibility, regulation, funding and education are challenges to overcome before progression can be made (Chan and Ginsburg, 2011, Weldon et al., 2012). Fully personalised medical care requires an individual's clinical, environmental, genetic and genomic information to inform medical decisions and tailor interventions; optimising disease prevention and treatment (Ginsburg and Willard, 2009).

In the UK clinical genetics has evolved from a small peripheral clinical service to an established multi-disciplinary service (Bleiker et al., 1997, Meiser et al., 2008, Grant et al., 2006). However numerous challenges exist today for the NHS clinical genetics service, particularly related to the provision of genetic counselling and testing services for patients with cancer or a family history of cancer (Burns, 2009, Evans et al., 2014, Skirton et al., 2014).

[3] Personalized medicine uses individual genetic and environmental information to prevent, diagnose and treat disease.

Genetic information will have significant impacts for the individual and their family, triggering psychosocial, financial and direct health consequences. Genetic and genomic tests cannot provide absolute predictions because a gene mutation alone cannot predict outcome; clinical interpretation that incorporates age and relevant lifestyle risk factors, and an understanding of test specificity and sensitivity is key when translating results and counselling patients (Hamburg and Collins, 2010, Gryn and Kim, 2014, O'Daniel et al., 2010).

Personal genomic information is not currently available via the NHS and access to genetic testing is restricted to those patients with the greatest clinical need[4]. The UK regulatory body, the Medicines and Healthcare Products Regulatory Agency (MHRA) and legal system provides protection to the British public from unscrupulous companies offering un-validated gene testing (HousesofParliment, 2012).

While there are barriers and opposition from some religious groups, to advancing Personalised Medicine many patients are requesting personalised care which takes a holistic approach to physical and mental health (Cornetta and Brown, 2013). The

[4] Direct-to-customer ancestry-related and un-interpreted raw genetic data is available from private companies such as 23andMe. ENNIS, C. 2012. Genetic screening: curiosity killed the CATG *The Guardian*, 11/10/2012.
Previously 23andMe offered health-related genetic reports, their most popular service, until in 2013 the American Food and Drug Administration (FDA) halted 23andMe from advertising and selling health-related reports. The FDA accused the company of misleading customers: DNA test kits did not have proven reliability therefore false results could result in individuals seeking treatment for diseases they do not have. Until the health-related DNA kit receives FDA approval as a medical device 23andMe will not be able to offer such a service. FUNG, B. 2013. Bowing again to the FDA, 23andMe stops issuing health-related genetic reports. *The Washington Post*, 6/12/2013.
Outwith the UK problems with un-regulated tests have resulted in unnecessary medical procedures and significant distress for patients. HAMBURG, M. A. & COLLINS, F. S. 2010. The Path to Personalized Medicine. *New England Journal of Medicine,* 363**,** 301-304.
Myriad Genetics, another private Bio-technology company, continues to offer worldwide private genetic testing. Myriad provide risk assessment and medical management recommendations for 8 cancers including breast cancer however the provision of this service appears to be in conjunction with the patient's physician.

psychology and personal experience of seeking genetic information requires carefully planned intervention that assist patients to make decisions and understand emotional reactions (McDaniel, 2005). Positive patient expectations, acceptance and willingness to receive and act on results are key to the future of personalised medicine (Cornetta and Brown, 2013).

Recently it has been proposed that behavioural and psycho-cognitive aspects are added to the 4P approach to oncology medicine (Pravettoni and Gorini, 2011). The 4P approach aims to create Predictive, Personalised, Preventative and Participatory models for patient care (Hood and Friend, 2011). This addition acknowledges the psychological impact of Personalised Medicine and is proposed with the aim of empowering the patient, a move from passive recipient to active decision maker. It is anticipated that the addition of a behavioural component yielded from personalised medicine has the potential to impact disease prevention, diagnosis, prognosis and treatments (Song et al., 2011, Jackson and Chester, 2014, Chan and Ginsburg, 2011). Table 1 details the proposed opportunities following complete adoption and integration of personalised medicine (PersonalizedMedicineCoalition, 2014). However the addition of lifestyle assessments and interventions will further impact disease and patient outcomes (Howell et al., 2014).

Table 1: The Potentials for Personalised Medicine

Opportunity	Example
Shift emphasis in medicine from reaction to prevention	Molecular markers to define disease risk or presence before clinical symptoms e.g. BRCA1 gene detection with subsequent prophylactic surgery or increased screening and chemoprevention.
Direct the selection of optimal therapy and reduce trial-and-error prescribing	Individual response to drugs varies due to genetic variation in enzymes or presence/absence of cell receptors e.g. HER2 receptors present in breast tumour tissue, instigate Herceptin therapy with the aim of reducing tumour recurrence.
Help avoid adverse drug reactions	Genetic variations in drug-metabolising enzymes can cause slow elimination and toxicity with effects ranging from unpleasant to fatal e.g. warfarin anticoagulant therapy.
Increase patient adherence to treatment	Effective treatment with few side effects or confirmed genetic risk for a conditions will incentivise therapy compliance.
Improve quality of life	Blood test for molecular marker to replace invasive diagnostic procedures e.g. lung cancer.
Reveal additional or alternative uses for medicines and drug candidates	Genetically defined patient population responses e.g. specific genetic mutation.
Help control the overall cost of health care	Target treatment to reduce costs e.g. early cancer diagnosis saving adjuvant chemotherapy, adverse event management and supportive care costs.

Source / Adapted from (PersonalizedMedicineCoalition, 2014)

The Personalised Medicine debate is acutely focused on highly penetrant genetic disorders (Jackson and Chester, 2014) and Genome-wide association studies (Lenfant, 2013) because it is within this area that the greatest benefit for the individual and healthcare can be realised. High penetrance confers a high lifetime risk for developing a condition[5]. The risk for individuals with these genetic mutations is rarely amplified by environmental or lifestyle factors and for the majority of these

[5] A disorder with 95% penetrance will affect 95% of individuals who have the mutation, i.e. the affected population will have a 95% chance of developing the disorder.

conditions the impact of the disorder is significant. Conversely low penetrance genes confer a low risk for developing the disease and risk is augmented with exposure to environmental factors (Shields and Harris, 2000)[6]. The highly penetrant BRCA1/2 genes have helped to facilitate research that aims to identify genomic information can be utilised for optimum patient benefit (Couch et al., 2014). Within the high penetrance paradigm genetic information identifies patients who will benefit from more intense screening and prevention therapies, including targeted treatments.

A 2010 publication (O'Daniel et al., 2010) reported results of a study that examined the opinions of experienced genetics health care professionals in relation to genomic testing, its apparent value, psychosocial impact and effect upon health behaviours. Fourteen participants undertook genomic testing, interviews and surveys. Motivation to (participate in the study and) acquire individual genomic information differed from a general population: professional curiosity and interest were reported by most participants and not a need to change unhealthy behaviours. Good health behaviours with a small 'margin for improvement' (p397) were reported. A small proportion of first responses to the personal genomic information were light-hearted with 'science nerd' (p392) qualities although the majority were positive and regarded the results as interesting however they did not indicate that the information was needed for health decisions.

[6] Using an example of sporadic lung cancer: cancer risk for low-penetrance genes, such as p53, is increased with exposure to carcinogens (e.g. tobacco).
SHIELDS, P. G. & HARRIS, C. C. 2000. Cancer Risk and Low-Penetrance Susceptibility Genes in Gene-Environment Interactions. *Journal of Clinical Oncology,* 18**,** 2309-2315.

Participants' perceived risk for disease both before and after the test was based upon family history; only 2 participants reported that genomic information influenced health risks after receiving results. The researchers in the O'Daniel study (2010) conclude that low risk results explain the low importance or impact of the results.

Genetic testing differs from genomic testing, it provides single gene information while genomics provide gene-wide or complete DNA sequence results. One participant confirmed that their health risk perception would change had single gene testing revealed a positive result. Corresponding health behaviour including information seeking was largely unchanged 3 months after receiving results, despite the majority of participants indicating pre-test that they may change health behaviour. The majority of participants report and the authors of the O'Daniel publication (2010) conclude that genomics will have more importance and significant potential in the future. While the characteristics of the participant group differ from a general population these findings are valid and assist understanding the value and health impacts of genetic and genomic information.

Individual Responses to Personalised Medicine

An individual's perceived risk of developing a disease and not scientific risk influences their behaviour, decision-making and emotional response (Lerman et al., 2002). From an individuals' first thought about obtaining genetic information, to their response to the results and proposed risk management interventions, the individual will require to make potentially life changing decisions (Finch et al., 2013, DeFrank et al., 2013).

The spectrum of diseases for which genetic testing is available ranges from progressive conditions, with no available treatment, to conditions for which preventative treatment can remove most of the risk for developing the disease. The psychology of genetic disease is recognised. McDaniel (McDaniel, 2005) reports that the experience begins with knowledge of the inherited condition within a family and that the testing experience is based in the meaning of the condition, or the individual's response to the genetic test results.

The decision to proceed with genetic testing is complex and emotionally laden. The individual's experience of caring for or loosing close family members, as a result of the condition for which genetic testing is under consideration, may further compound the psychosocial impact of decision making. A recently published review of psychosocial reactions to predictive genetic test results indicates three areas of impact:

- altered social relationships
- important life decisions such as career
- reproductive choices and self-concept (Grubs et al., 2014).

These authors however provide reassurance that negative consequences, for example severe depression impacting on all aspects of life, for the participants were not as severe as initially predicted. Graceffa and colleagues (Graceffa et al., 2009) caution against genetic testing without psychological support for individuals who have specific psychological traits, such as prior mental health problems. Genetic identification of an individuals' risk for developing a condition or disease may create potential isolation, stigma and exclusion impacting for a wide range of social

relationships ranging from employer, financial institutions and companies, health care professionals, family members and spouse / future spouse.

Stigma and isolation have particular relevance in the case of highly penetrant defects which confer a significant lifetime risk for developing the condition, such as BRCA1 which confers up to an 80% lifetime risk. Furthermore an individual may be looked upon or treated as if they have developed the disease, or that their destiny is to even develop the disease when gene penetrance or the risk of developing the condition is not understood (Novas and Rose, 2000)[7]. An example highlighting such difficulties is described by Kitzman and Sweeny; sensitive genetic information may not be communicated to a potential partner; with fear of rejection or previous personal experience are cited as reasons for non-disclosure (Klitzman and Sweeney, 2011)[8].

Diverse family relationships will be impacted by the knowledge of a genetic condition and in relation to genetic inheritance past and future. Contribution to another individual's risk for developing a disease affects relationships between parents,

[7] Consider Huntington's Disease: the individual identified as a carrier and would not be expected to develop the disease however an insurer may decline to provide life insurance because they do not appreciate the individual has a very low risk for developing the disease. Conversely a highly penetrant BRCA defect: where a woman who has received breast cancer specific genetic information then undertakes risk reducing bilateral mastectomy surgery to minimise her chance of developing breast cancer has arguably increased her lifespan however suffers social stigma associated with mastectomy.

[8] Outwith the scope of this project but worth a brief mention are the following social impacts that relate to molecular genetics:

- The growing belief that many 'undesirable conditions' have a basis in a genetic mutation. This psychosocial impact may create added stress for an individual undertaking genetic testing or following the receipt of results that confirm the presence of a mutation. On a more positive note it is however often easier to gain research funding for 'undesirable' diseases
- Does genetic information reduce the individual to cellular matter? This question relates to human identity or the notion of being human, a personal and global level
- Governance for molecular genetic science to ensure that individuals are protected, for example to ensure that inadvertent identification of genetic mutation through diagnostic screening tests does not occur.

siblings, partners and children (MacDonald et al., 2010, McDaniel, 2005). MacDonald (2010) explores the impact on family relationships citing the potential for genetic information to sub-divide families. Conversely the family social network may be enhanced, in response to genetic counselling and the identification of new family members, or the current family structure may be enriched in respect of new found genetic inheritance (Novas and Rose, 2000).

Graceffa et al (2009) relates coping mechanisms used during the pre-symptomatic genetic test process with psychological mechanisms used by individuals during Post Traumatic Stress Disorder. The use of avoidance, in order to prevent thoughts about the disease was used by a high proportion of participants in their study, particularly before test results were received. Avoidance affects relationships when the individual avoids close emotional relationships. Emotional numbness, a symptom of avoidance, will be characterised by the individual performing routine activities that require little engagement. Later when thinking about the testing process, flashbacks may occur when the individual may be flooded with emotion or correspondingly they may be incapable of feeling or expressing the emotions relating to their psychological response to genetic testing (Graceffa et al., 2009). These authors report depression as a common response to unresolved emotional pain. Extreme psychosocial responses were only reported by female participants.

Emotional responses including anger, sadness and guilt are recognised reactions to carrying and passing a genetic mutation to family members (McDaniel, 2005). Depression and anxiety following positive results can be related to guilt and concern for family members (Graceffa et al., 2009). Regardless of cause depression and

anxiety will affect an individual's quality of life. Graceffa (2009) reports a negative impact on general well-being following positive genetic test results. Furthermore the authors propose that loss of social functioning and reduced self-esteem, may be in response to fear of disease or becoming a burden for the family.

Psychological response to a negative results include regret about not living life to the full while living with a high risk of developing an inherited disease (McDaniel, 2005). This is frequently likened to 'Survivor guilt' (Valverde, 2006, McDaniel, 2005, Graceffa et al., 2009, Cummings, 2000). Survivor guilt in this context is a psychological reaction that occurs in response to the confirmation that an individual does not carry a genetic mutation, while other family members are affected. This guilt can relate to relief or joy, that is felt when results are revealed or later when the individual feels a new sense of freedom, then subsequently has to deal with the reality of a disease that affects other family members (Graceffa et al., 2009).

Psychological support is recommended both before and long-term after genetics testing, irrespective of the result (Graceffa et al., 2009). Efforts have been made to predict outcomes to genetic testing, with complex pre- and post-test assessment and counselling in use for Huntington's Disease (Grubs et al., 2014), to ensure that individuals are fully informed about testing and receiving their results.

In the last 10 years a multi-disciplinary team in Wales have conducted several studies that revealed the psychological and emotional responses to cancer genetic-specific information. In response to the findings they developed a measure of coping tool: GRACE (Phelps et al., 2010). The tool acknowledges 2 main coping styles (as

reported by Miller (Miller, 1995) although terminology differs) and is based on 11 areas of concern or stress and 8 coping strategies, that were identified in their earlier work, these are presented in Table 2. These stressors and coping strategies are commonly reported across genetic testing (regardless of clinical area / indication) and psychological support text (Graceffa et al., 2009, Dougall et al., 2009, Smith et al., 2008).

Table 2: GRACE Tool Stressors & Coping Strategies

11 Stressors	**8 Coping Strategies & Examples**
Not understanding the risk assessment process	Acceptance: Accepted nothing I can do
Having to wait to find out my risk	Distraction: Did things to take my mind off it
Completing the Family History Questionnaire	Positive appraisal: Focused on the positive aspects
Asking family members about cancer in the family	Planning: Made and followed a plan of action
How I would cope if found to be at increased risk	Information seeking: Searched for more information about it
How family members would react if found to be at increased risk	Social support: Sought support from family and / or friends
Being eligible for genetic testing	Emotional expression: Talked or wrote about it / what I felt
Possible decisions about surgery	Role model: Though of positive role models
Being able to get increased screening	
The impact on my lifestyle if found to be at increased risk	
The implications for family members if at increased risk	

Source / Adapted from (Phelps et al., 2010, Bennett et al., 2012)

The team have recently presented the results of a randomised study, that used the tool to explore patients concerns and coping before and during cancer genetic risk

assessment (Bennett et al., 2012)[9]. The greatest concern for participants was future consequences of being at high risk, both on a personal and family level. A range of coping strategies were reported for each concern however all strategies were employed in response to all concerns at baseline and 1 month follow-up. Emotional strategies (positive appraisal, acceptance, social support) were used most often during the risk assessment period, when the patient waited and little could be done to change the concerns. The authors propose that genetic counsellors use the GRACE tool to focus counselling.

Genetic mutations alone do not predict disease outcomes. To quote one Harvard psychology professor “actual outcome depends on a tangle of other circumstances” (paragraph 14) (Pinker, 2009). The majority of ‘other circumstances’ are arguably health behaviours and these are the source of much debate. Increasing availability of genetic information, through single gene or genome testing, can provide individuals with disease susceptibility knowledge however positive health behaviours are required to moderate future health-problems.

Much of the early patient research relating to the psychological aspects of single gene testing has been carried out with the hereditary breast and ovarian cancer, hereditary colon cancer and Huntington’s Disease populations. However research with a specific health behaviour focus is primarily focused on hereditary cancer populations, where positive lifestyle change can alter risk for developing disease (Beery and Williams, 2007). Publications in 2010 and 2012 reinforce the findings in

[9] In using the Grace Tool the patient scores their frequency of worry from 0 (not at all) to 3 (very much so) for each of the worries then indicates which of the coping strategies they have used (either done or thought about) for each.

Beery and Williams earlier systematic review and make the observations, that where genetic information confirms a low risk for developing the condition of interest health behaviour will be largely unchanged, and correspondingly, where risk is high positive health behaviours will be adopted (McBride et al., 2012, McBride et al., 2010). These findings relate primarily to screening behaviours for highly penetrant genetic conditions and not to exposure health behaviours (e.g. smoking, exercise, healthy diet) which have limited effect on development of highly penetrant disease. Irrespective of the study population, research shows, a wide variation in health behaviour change in response to personalised genetic and genomic information (Schneider and Schmidtke, 2014). Within the global population the most common causes of ill health and mortality are related to unhealthy behaviours such as smoking, high alcohol consumption, over-eating and under exercising. Within populations with a genetic mutation that confers an increased risk for disease, the complex interaction of such unhealthy behaviours further compound individual risk (Boyle, 2012, Guinan et al., 2013b, Bao et al., 2013, Hu, 2011).

Nevertheless, the previous 20 year increase, current and projected rise in breast cancer incidence is not unexpected (Howell et al., 2014). Healthy lifestyle choices in the three key areas (weight control, regular exercise and modest alcohol intake) could cut breast cancer risk by approximately 30% (Howell et al., 2014). Exposure to these and other modern lifestyle risk factors may be attributed to the increase in breast cancer risk found in high risk families: in a UK study population women born after 1960 had a 40% risk for breast cancer by age 40 while those born in 1940 had

a 22% risk by age 40 compared to only 8% in the group born before 1930 (Evans et al., 2008)[10].

One investigation, that presented participants with hypothetical genetically-linked disorders, reported a higher risk for developing a disorder correlated with greater intention to adopt recommended health behaviours. However there was no evidence to suggest the genetic information is a stronger motivator than family-history based risk information (Hicken and Tucker, 2002). Expectations that genetic information will motivate positive health behaviours have been explored for several decades. Reports suggest that genetic risk information, may be the least useful health risk information, when health behaviour change is required (Marteau and Weinman, 2006).

The potential use of genetic testing as a motivational tool within complex diseases has been studied using the paradigm of smoking cessation (Sanderson and Wardle, 2005). This study reported that 65% of participants would be motivated to stop smoking following the receipt of a positive genetic test result however 39% would be discouraged to stop should they receive a negative result. Similar findings have been reported in hereditary breast and ovarian cancer studies with patients undertaking prophylactic surgery in response to positive BRCA genetic test results (Tercyak et al., 2007, Schwartz et al., 2003, Watson et al., 2004).

[10] The authors report similar parity and age of onset for menarche and menopause across the age groups.

The previously described work of O'Daniel et al (O'Daniel et al., 2010) reported minimal change to lifestyle or health behaviours in response to genetic information however the research population, genetic health care professionals, differs considerably from a general patient population. There is concern that genetic risk information may discourage positive health behaviours (McBride et al., 2010, Grant et al., 2011, Graves et al., 2014, McBride et al., 2012) and this is particularly relevant when considering direct-to-consumer genetic testing (Bloss et al., 2011), for example when results indicate a low risk for cardiovascular disease and subsequently motivation to adopt a healthy diet or stop smoking is decreased. A modest 27% change in health behaviour is reported in a study that investigated health behaviour and anxiety in a direct-to-customer genetic test population (Egglestone et al., 2013). Personalised genetic information and kinship networks have been proposed to encourage health behaviour change (McBride et al., 2010). Exploitation of familial networks may increase the motivating effect of genetic information, while shared risk and peer pressure can promote continued focus.

The ethical issues that relate to gene testing have a long history and are far-reaching. Much of the early debate relates to predictive testing for hereditary adult-onset disease such as Hereditary Breast and Ovarian Cancer (HBOC), Cardiomyopathy and Huntington's Disease (HD). When consideration is given to genetic testing, often for healthy, individuals who have a family history of adult onset disease the ethical debate encompasses much of the lifespan. Individuals who carry a gene mutation that predisposes them to adult onset disease have concerns about passing the mutation to their children, this is particularly so with an autosomal dominant pattern of inheritance, for example HBOC or HD, where each child has a

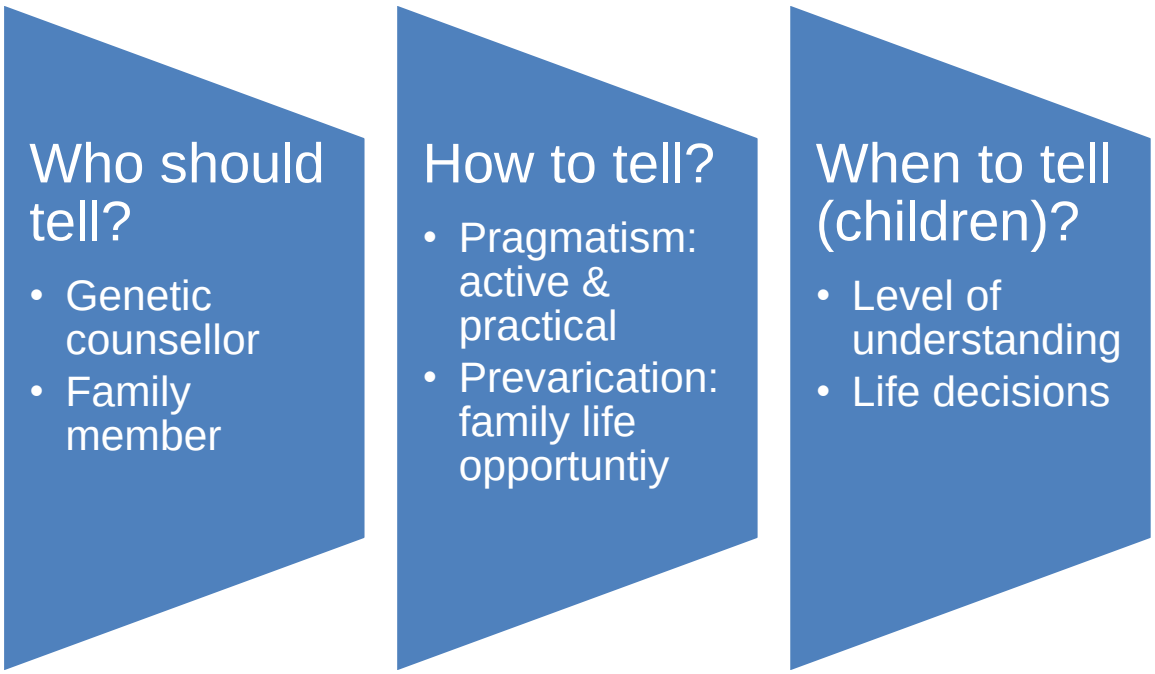
50% chance of inheriting the mutation (Donnelly et al., 2013, Decruyenaere et al., 2007). Child bearing decision making is one of the frequently cited reasons for undertaking genetic testing for hereditary cancer (Pasacreta, 2003). Questionnaire studies that explore reproductive decisions report between 12% (HBOC) and 35% (HD) participants choosing not to have children in response to their confirmation of a genetic mutation that conferred a high risk for adult onset disease (Fortuny et al., 2009, Decruyenaere et al., 2007).

Disclosure of information, to relatives, that creates worry causes ethical discord, for example cancer risks (Hallowell et al., 2003). The study participants described experiencing conflict, associated with their responsibility to care for family members, when the genetic information would be portrayed (by or for the relative) as a new or increased health risk. Not talking about the result to avoid upset for the family member, has been described as increasing isolation for the individual with the gene mutation (Foster et al., 2004), and negative health implications may result when a family member is not informed of their potential genetic risk (Pho et al., 2000). Appropriate health screening and prophylactic choices that are available to at risk individuals may not be considered or available when the risk is unknown.

Moral and ethical considerations relating to informing a relative of risk, when the individual tested has no contact or when privacy for the individual tested is requested, will have psychological impacts for the individual tested, the family and the geneticist or genetic counsellor. Decisions about revealing genetic information to family members are described in a qualitative interview study of 37 individuals and 19 partners, facing HBOC and HD (Forrest et al., 2003). Disclosure was identified

as difficult for some participants. There main difficulties are identified, these are presented in Figure 2. Many participants identify that the family are responsible for informing relatives about a potential genetic risk. However health care professionals are thought by some to legitimise or back-up uncertain risk information. It is notable that regardless of who in the family receives the genetic information the majority assume the role of informing children of potential risk is primarily that of the parents. Difficulties may arise when informing a niece or nephew.

Figure 2: Genetic Disclosure Difficulties



Source / Adapted from (Forrest et al., 2003)

Disclosure is considered a process, and not a single, act with two styles: 'pragmatism' and 'prevarication' (pg 321) (Forrest et al., 2003). Pragmatic individuals take an active and practical approaches. Prevaricators search for normal 'family life' opportunities where 'the right moment' is identified for disclosure (pg 321); this can

take a long time. Problems may arise when both styles of disclosure exist within the family and one member may feel rushed into sharing the information.

The best time to tell is presented when the first important disease-related life decision needs to be made, for example when a child forms a serious relationship / considering having children or when cancer screening / prophylactic intervention can start. Another key time identified is when a child is considered old enough to understand the information (e.g. early teenage years). The authors acknowledge that genetic health care requires understanding of subtle family issues, to assist people to come to terms with the emotional and ethical issues relating to a genetic disorder (Novas and Rose, 2000).

Personalised Medicine Challenges

Personalised Medicine approaches are being integrated within oncology. Ethical and social challenges, of oncology specific personalised medicine, have recently been published in a study that explored the perspectives of 117 institutional and professional stakeholders. This research report, by McGowan et al (2014), demonstrates recent integration and discusses the associated ethical challenges. The authors conclude with 4 significant ethical concerns (displayed in Figure 3). McGowan focuses on targeted oncology therapies and healthcare costs for up-scaling pharmacogenomic testing. While these concerns exist currently within the oncology paradigm the authors propose they will extend into new clinical areas, as PM approaches evolve and integrate (McGowan et al., 2014).

Figure 3: Personalised Medicine - the Ethical & Social Concerns

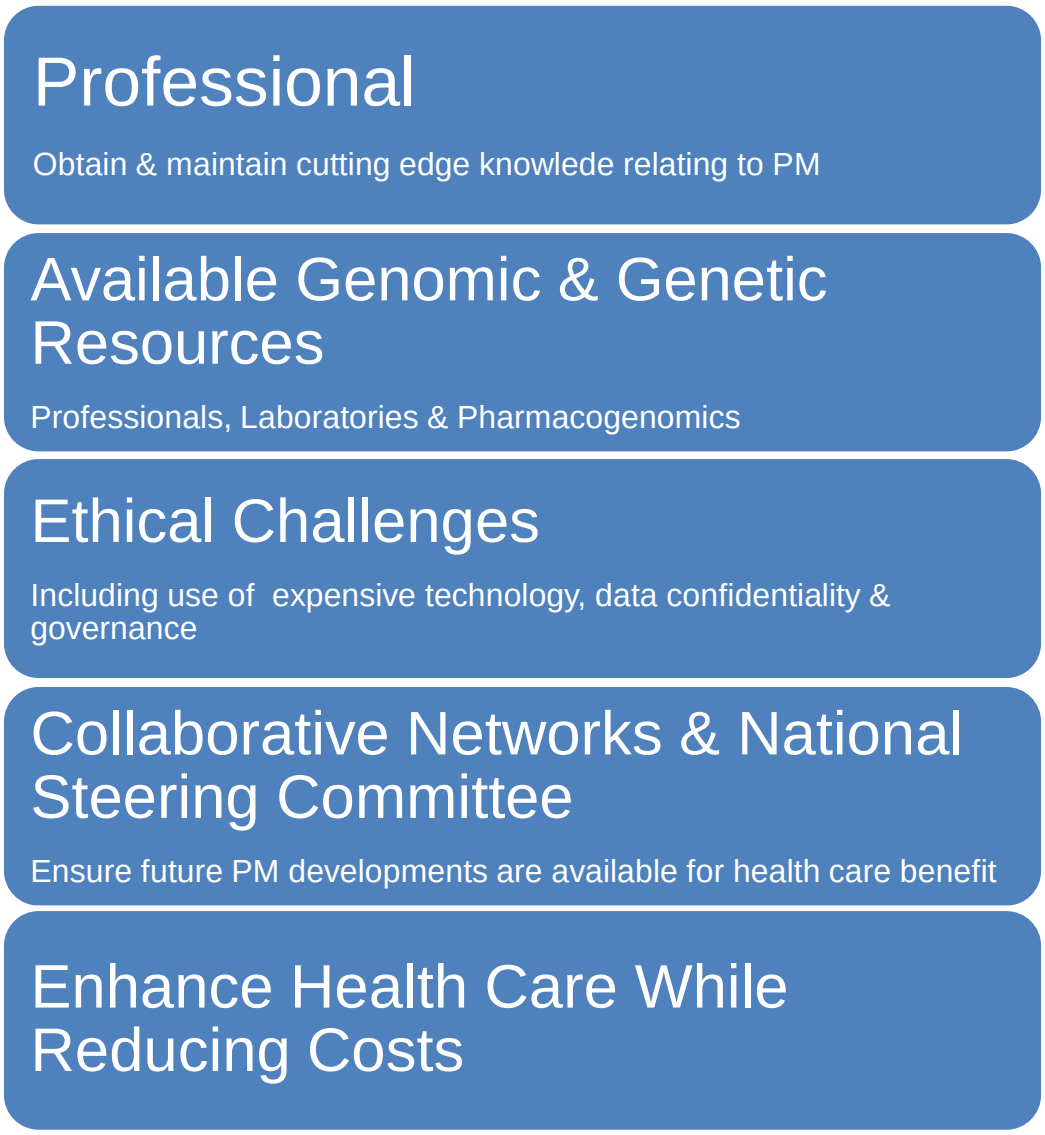
Source / Adapted from (McGowan et al., 2014)

A more recent review of ethical, legal and social challenges (Joly et al., 2014) expanded the McGowan et al (2014) findings to provide patient safeguards. Key challenges include:

1. Protection for individuals and sub-populations to ensure that they are not discriminated against
2. Emerging healthcare roles
3. Clinical translation of results and therapies
4. Direct-to-consumer testing.

Similarly a manuscript published in 2013 identifies additional obstacles for personalised medicine and makes recommendations, these are detailed in Figure 4.

Figure 4: Recommendations for Personalised Medicine



Source / Adapted from (Cohen, 2013)

A study that explored patient and staff perceptions of privacy and equality during diagnostic genetic testing revealed differing patient and staff opinions. The authors concluded that genetics staff require additional ethics training, and that counselling should consider the patient from a global perspective (Nyrhinen et al., 2007)[11].

[11] UK confidentiality laws forbid doctors from disclosing genetic test results to other interested parties, this includes relatives. The responsibility for communicating genetic information, to potentially affected family members, lies with the individual tested. HALLOWELL, N., FOSTER, C., EELES, R.,

Clinicians are responsible for the identification of suitable patients for gene testing, however this role requires knowledge and patient advocacy skills when gene testing is challenged, for example due to resource allocation. Additionally advocacy will be required where barriers to care provision result, for example within personalised medicine gene specific drug treatment is frequently more costly than standard care however patient benefit is also greater. Collaboration and teamwork with associated clinical specialities are crucial to the success of the genetics. It is essential that these colleagues support and acknowledge the evolving role of the genetics for patient care benefit.

The provision of emotional support, risk information and risk reduction treatments are frequently a source of ethical dilemma for health care professionals (Burke and Press, 2006). A survey of genetic service health care professionals revealed the most common ethical problems correspond to patient's emotional reactions, informed consent, uncertain test results and limited resources (Abad-Perotín et al., 2012). The clinician shares the patient's burden to ensure autonomy and informed choice are provided for the patient and at risk members of the family. Reassuringly these authors report that such ethical dilemmas occur very infrequently.

ARDERN-JONES, A., MURDAY, V. & WATSON, M. 2003. Balancing autonomy and responsibility: the ethics of generating and disclosing genetic information. *Journal Of Medical Ethics,* 29**,** 74-79.

The General Medical Council (GMC) acknowledges that some patients may refuse to share genetic information and recognises that in exceptional cases disclosure, that where possible does not identify the index patient, may be justified. GENERALMEDICALCOUNCIL. 2009. *Confidentiality guidance: Genetic and other shared information* [Online]. London: GMC. Available: http://www.gmc-uk.org/guidance/ethical_guidance/confidentiality_67_69_genetic_and_other_shared_information.asp [Accessed 11/02/15 2015].

These exceptional cases must be weigh-up potential harm both to the patient and patient–doctor relationship from disclosing the index patient's information and that caused by non-disclosure to the relative. The role of the genetics health care professional extends to adopting a proactive stance to support individuals to share genetic information with relatives. At times this role will include facilitation of family communication however the principles of privacy and autonomy should not be compromised. SUTHERS, G. K., ARMSTRONG, J., MCCORMACK, J. & TROTT, D. 2006. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *Journal Of Medical Genetics,* 43**,** 665-670.

5.3 Breast Cancer & Genetics: The Size of the Problem

Excluding age, family history or genetic inheritance is one of the most fundamental factors in determining breast cancer risk (Antoniou and Easton, 2006). Approximately 5-10% of all breast cancers are associated with a hereditary predisposition (Lynch et al., 1984, Claus et al., 1996).

A Case for Breast Cancer Genetics

BRCA1/2 mutations occur in around 2 in 1000 of the general population (ABCSG, 2000)[12]. This incidence is confirmed by a large scale re-analysis study that included 52 epidemiological studies and just under 15,000 patients. This study reported just over 0.1% of the general population or 1 in 450 women carry a fault in either the BRCA1 or BRCA2 gene (CGHFBG, 2001).

Reports, previous and current, estimate that mutations in the two highly penetrant BRCA genes, account for between 5 and 10% of breast cancer in the general population (Kiberstis and Roberts, 2014, Claus et al., 1996). The variations in these estimations indicate that additional genes (Couch et al., 2014, Shuen and Foulkes, 2011, Smith et al., 2006b, Begg et al., 2008, Ponder et al., 2005)[13] and modifiable

[12] Breast cancer incidence supplementary information is provided in Appendix A.

[13] The identified breast cancer susceptibility genes are categorised into three groups:

- high-penetrance alleles e.g. BRCA1, BRCA2 and TP53
- rare medium-penetrance alleles e.g. CHEK2 and ATM
- common low-penetrance alleles e.g. FGFR2 and TOX

WOOSTER, R. 1995. Identification of the breast cancer susceptibility gene BRCA2. *Nature,* 378**,** 789, MIKI, Y. 1994. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science,* 266**,** 66, WALSH, T., CASADEI, S., COATS, K. H., SWISHER, E., STRAY, S. M., HIGGINS, J., ROACH, K. C., MANDELL, J., LEE, M. K., CIERNIKOVA, S., FORETOVA, L., SOUCEK, P. & KING, M.-C. 2006. Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer. *JAMA: The Journal of the American Medical Association,* 295**,** 1379-1388, STRATTON, M. R. & RAHMAN, N. 2008. The emerging landscape of breast cancer susceptibility. *Nat*

lifestyle factors may be involved (King et al., 2003, Nkondjock and Ghadirian, 2004, Guinan et al., 2013a, Colditz and Bohlke, 2014).

Individuals with an affected first-degree relative (i.e. mother or sister) have a two-to threefold increased risk of developing breast cancer over the general population (Malone et al., 1998, Kerlikowske et al., 1992, Pharoah et al., 1997), this risk further increases where two or more relatives have been affected and where the relative was diagnosed below age 50 (CGHFBG, 2001). Up to 15% of invasive breast cancer is diagnosed in women with at least 1 first-degree relative (mother, sister or daughter) who has / had breast cancer (Møller et al., 2007).

Approximately 80% of patients with familial breast cancer do not have BRCA1/2 gene mutations (Thompson and Easton, 2004). Estimates do however vary, Moller reports that family history investigation exposes fewer than 50% of BRCA1/2 mutation carriers (Møller et al., 2007) while other investigations state that the presence of mutations in the BRCA1/2 genes, account for between 10-40% of hereditary breast cancer (Walsh et al., 2006, Shuen and Foulkes, 2011, Antoniou et al., 2003). Given that BRCA1/2 gene mutations are not indicated in the majority of hereditary breast cancer cases, it is reasonable to conclude that familial breast cancer requires further exploration. Nevertheless women with a significant family history who present with breast cancer are most likely have a highly penetrant BRCA1/2 mutation (Eccles and Pichert, 2005) and the majority of women with

Genet, 40**,** 17-22, GUDMUNDSDOTTIR, K. & ASHWORTH, A. 2006. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene,* 25**,** 5864-5874, ibid.

BRCA1/2 mutations have in their family a history of BRCA-related cancers (Francken et al., 2013).

In the last 2 decades over 1800 distinct variants of BRCA1 mutation and in excess of 2000 in BRCA2 variants have been identified and the associated risk for developing cancer calculated, reported in (Couch et al., 2014)[14]. Whole genome information is not available for the vast majority of patients, genetic information specific to hereditary breast cancer can be used to assess risk, plan preventative measures and predict responses to treatment (Vig and Wang, 2012, Couch et al., 2014).

BRCA1/2 mutations are by far the most common cause of hereditary breast cancer (Miki et al., 1994, Wooster et al., 1995), accounting for approximately 20-25% of familial breast cancer and in families with four or more breast cancers BRCA1/2 account for the majority of cases (Ford et al., 1998, Peto et al., 1999, Easton, 1999, ABCSG, 2000, Eccles et al., 2000). Correspondingly, the majority of women with hereditary breast cancer will not be found to have a BRCA1/2 mutation (Thompson and Easton, 2004, Eccles and Pichert, 2005). For these women genetic testing may reveal a BRCA mutation of uncertain significance or no mutation. BRCA gene variants of uncertain (or unknown) significance are DNA alterations for which there is insufficient data to categorise the alteration as harmful, indicating increased cancer risk[15] (Cheon et al., 2014). For women who present with a triple negative tumour

[14] Predictive genetic testing (prior to breast cancer diagnosis) has been available for approximately 20 years however at that time was expensive and the waiting time for results was lengthy. In the early years accuracy of testing was poor and targeted screening was required in order to locate known mutations within a family or founder group such as the Ashkenazi Jewish or Dutch populations.

[15] Further genetic investigation will be proposed to establish cancer risk where a previously unidentified or rare variant is identified. It is proposed that the majority of uncertain significance

around 20% will not reveal a BRCA1/2 mutation (Lakhani et al., 2002). Personalised treatment and risk reduction pathways for these patients will rely on genetic risk predictions and tumour biological characteristics (Boyle, 2012, Huzarski et al., 2013, Rhiem et al., 2012).

BRCA1/2 related breast cancer diagnosis is more likely where the patient is from a known high risk group (Antoniou et al., 2003, Thompson and Easton, 2004, Jackson et al., 2014):

- member or descendent of an ethnic group with a known founder BRCA1/2 mutation such as Ashkenazi Jewish (Struewing et al., 1997, Roa et al., 1996), Icelandic and Polish origins (Hodgson, 2007)
- family history of the following cancers: breast, ovarian, prostate, thyroid, sarcoma, endometrial, adrenocortical, brain or pancreas (Cybulski et al., 2014, Marsh and Zori, 2002, BreastCancerLinkageConsortium, 1999).

In families where a BRCA1/2 mutation is present there will be mutation-positive and mutation-negative members. In the largest prospective study of mutation-negative

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results will not confer increased risk ECCLES, D. M., MITCHELL, G., MONTEIRO, A. N., SCHMUTZLER, R., COUCH, F. J., SPURDLE, A. B. & GOMEZ-GARCIA, E. B. 2015. BRCA1 and BRCA2 genetic testing-pitfalls and recommendations for managing variants of uncertain clinical significance. *Ann Oncol*.. Additionally the proportion of uncertain results are reducing; MYRIAD reported uncertain significance in 12.8% of BRCA1/2 tests in 2002, this rate fell by 77.3% to 2.9% of tests in 2012 EGGINGTON, J., BURBRIDGE, L., ROA, B., PRUSS, D., BOWLES, K., ROSENTHAL, E., ESTERLING, L. & WENSTRUP, R. Current variant of uncertain significance rates in BRCA1/2 and Lynch syndrome testing (MLH1, MSH2, MSH6, PMS2, EpCam). Presented American College of medical genetics and genomics annual meeting, 2012.. International collaborative groups, such as ENIGMA, which facilitate the collection and (re-) classification of rare and previously unidentified variants aim to improving clinical knowledge and patient management SPURDLE, A. B., HEALEY, S., DEVEREAU, A., HOGERVORST, F. B., MONTEIRO, A. N., NATHANSON, K. L., RADICE, P., STOPPA-LYONNET, D., TAVTIGIAN, S., WAPPENSCHMIDT, B., COUCH, F. J. & GOLDGAR, D. E. 2012. ENIGMA--evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. *Hum Mutat,* 33**,** 2-7.

women, from families with BRCA1/2 genetic mutation, the data indicated that breast cancer risk for mutation-negative women is similar to the general population risk, with a slight increase, where there is a family history of breast cancer in a first degree relative (Korde et al., 2011).

Diagnosis, Recurrence, Prognosis & Treatment

The likelihood of breast cancer diagnosis increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically (Aaronson et al., 2010). Women with a family history of breast cancer are most likely to be diagnosed with breast cancer over the age of 50, despite the risk of diagnosis being greater when they are under 50 (CGHFBG, 2001). The lifetime risk by age 70 for developing breast cancer with a mutation in the highly penetrant BRCA1 or BRCA2 genes is 45 to 88% (Antoniou et al., 2003, Walsh et al., 2006, Ford et al., 1998). Age of diagnosis with a BRCA1/2 related breast cancer is attributed at the rate of approximately 33% of cases in the 20-29 age group, decreasing markedly with age to 2% of cases in the age 70-79 range (Claus et al., 1996).

The risk for BRCA1 and BRCA2 are similar however it has been reported that for BRCA2 breast cancer risk is lower in the under 50 age group (Ford et al., 1998). The presence of a BRCA1/2 mutation increases the risk for early onset and bilateral breast cancer (Korde et al., 2011). In addition women with a BRCA1/2 mutation face an approximate 15-60% risk of ovarian cancer (Ford et al., 1998, Struewing et al., 1997, Easton et al., 1995, Ford et al., 1994).

A critical review of evidence, published in 2010, states that BRCA mutation carriers have a significant risk of contralateral recurrence and at 10 years recurrence occurs in 20-40% of carriers (Bordeleau et al., 2010). The risk for BRCA1 mutation carriers of contralateral cancer is reportedly higher than for BRCA2 mutation carriers (Graeser et al., 2009). However a longitudinal study, carried out by the Rotterdam Family Cancer Clinic, reports high contralateral recurrence risk as the only clinical outcome difference when BRCA2 mutation related cancers are compared with non-BRCA sporadic cancers (Brekelmans et al., 2007).

Prognosis for BRCA1/2 mutation carrier is not clearly defined (Robson et al., 2004). Studies cite similar (Liebens et al., 2007, Pierce et al., 2010, Rennert et al., 2007, Bordeleau et al., 2010), worse (Foulkes et al., 1997, Chappuis et al., 1999) and improved prognosis (Marcus et al., 1996) when compared to sporadic breast cancers. Significant for prognosis, the patient has an increased risk of developing ovarian cancer where BRCA1/2 mutation is detected (Easton et al., 1995, Peto et al., 1999, Miki et al., 1994).

A meta-analysis and review of survival patterns, conducted by Lee et al in 2010, advises 5-year recurrence and overall survival are reduced in BRCA1 mutation carriers but both are improved in BRCA2 mutation carriers when compared with non-hereditary breast cancer patients: this is attributable to distinctive BRCA1 and BRCA2 carcinogenic pathways (Euhus and Robinson, 2012, Lee et al., 2010).

Approximately 80% of BRCA1 mutation-related breast cancers are triple-negative (ER, PR, HER2) while 75% of BRCA2 associated tumours are hormone responsive

or receptor positive (Peto et al., 1999, Schwartz et al., 2008) (Lakhani et al., 2002, Lips et al., 2013). Triple negative breast cancer has a poorer prognosis than tumours with positive receptor status (DeRuijter et al., 2011). When combined with the 70-80% chance of a triple negative breast cancer, the overall the risk of recurrence is higher and prognosis is worse for women with a BRCA1 mutation related breast cancer (Stratton, 1997, Eccles and Pichert, 2005, Stoppa-Lyonnet et al., 2000).

The Rotterdam Family Cancer Clinic reported, an identical clinical course and overall prognosis for 103 BRCA2 mutation carriers when compared with non BRCA1/2 and sporadic breast cancer (Brekelmans et al., 2007). A recently published, international population-based cohort study, concludes that outcome for BRCA2 mutation carriers is related to more unfavourable biological tumour characteristics rather than mutation status (Goodwin et al., 2012).

The benefit of treatment tailored to genetic status and tumour characteristics was identified in the mid-2000s however the challenge that lay ahead was to identify the most appropriate treatment specific for BRCA1/2 related breast cancer (Daly, 2004). Evidence-based clinical guidance for the treatment of BRCA1/2 related breast cancer until the mid-2000s was poor (Eccles and Pichert, 2005, Liebens et al., 2007).

Clinical Guidelines

Women in the UK from families with a strong history of breast and / or ovarian cancer have, since the late 1990s, been able to access specialist family history

breast clinics (Saunders et al., 1999)[16]. Family History Breast Cancer Clinics (FHBCC) offer multi-disciplinary care and screening from genetics, radiography, medicine, surgery and nursing services. Women attending the FHBCC have a moderate to high risk of developing breast cancer. The NHS Tayside FHBCC works to Scottish Government Guidelines. Table 3 details stratification and management for women with a family history of breast cancer.

Within a family history surveillance programme breast cancer occurs at a rate of 6 per 1000 annual examinations; an eleven year study (1995-2006) of the NHS Tayside FHBCC surveillance programme reported cancer detection in 5.8 per 1000 screening examinations (Reis et al., 2009). Of these 74% were detected at screening with 78.5% detected at an early stage (Reis et al., 2009).

Improvements over the last 10 years in scientific knowledge, molecular genetic techniques, clinical genetics and cancer services have enabled gene testing to be incorporated into routine clinical practice for patients with an indicative family history or clinical features that suggest BRCA1/2 gene mutation (Eccles and Pichert, 2005). Today predictive testing is accurate, faster and cheaper than in previous decades however the UK clinical guidelines threshold for testing exclude many women (NICE, 2013b, ScottishGovernment, 2013).

[16] UK breast care services supplementary information is provided in Appendix B.

Table 3: Management of Women with a Family History of Breast Cancer

	Moderate Risk	High Risk
Stratification	1 first degree relative with breast cancer diagnosed < age 40 OR 1 first degree relative with male breast cancer (any age) 2 first or 1 first & 1 second degree relative with breast cancer diagnosed < age 60 OR ovarian cancer at any age on the same side of the family 3 first or second degree relatives with breast or ovarian cancer in the same side of the family where 1 is a first degree relative of the proband[17] OR of the proband's father Bilateral breast cancer is equivalent to 2 affected relatives First degree = mother, sister, daughter Second degree = Grandmother, granddaughter, aunt, niece.	Families with 4 of more relatives with breast cancer < age 60 OR ovarian cancer at any age, in 3 generations Families where one individual has had breast and ovarian cancer Families where there is an estimated 20% likelihood of BRCA1/2 or p53 mutation Individuals with a lifetime risk of developing breast cancer of ≥30%. Individual being assessed should be a first degree relative of an affected family member or a second degree relative through an unaffected male Affected individuals should be first degree relatives of each other or related through unaffected males.
Surveillance	Start age 40 or 5 years younger than the youngest age of cancer onset in family Mammogram 2 yearly < age 40; annual mammogram age 40-50 Mammography should not usually commence before 35, all women in this group should be offered mammography by age 40 Breast examination where possible, may be appropriate before age 35 when family history of early onset cancer.	Start age 35 or 5 years younger than the youngest age of cancer onset in family Mammogram 2 yearly < age 40; annual mammogram age 40-50; 18 monthly age 50-70 Mammography should usually start age 35, & should not be offered below age 30 Breast examination should be offered, particularly to women considered too young for mammography who have come from families where onset of cancer < age 35 Genetic testing should be offered in these families, if a sample is available from an affected relative. Where mutation testing cannot be offered the possibility that the woman may be at sufficiently high risk to be offered MRI should be considered.

Source / Adapted from Chief Medical Officer & Public Health Directorate 2009 publication: Cancer Genetics Services in Scotland - Management of Women with a Family History of Breast Cancer (Burns, 2009).

[17] Proband: individual being investigated. Usually the first affected family member to bring the genetic disorder to medical attention. Source NATIONALHUMANGENOMERESEARCHINSTITUTE. 2014. *Proband* [Online]. National Institutes of Health. Available: http://www.genome.gov/glossary/index.cfm?id=164 [Accessed 9/6/14 2014].

Clinical guidelines identify individuals who are most likely to benefit from BRCA1/2 gene testing (ScottishGovernment, 2013, NICE, 2013c, NICE, 2013b). Patients who present with a significant or 10% risk of carrying a BRCA1/2 mutation should be referred to Clinical Genetics for detailed assessment (Schwartz et al., 2008). Table 4 summarises clinical guidance for Clinical Genetics referral.

Table 4: Candidates for Genetic Referral

Early breast or ovarian cancer onset, before age 40
Multiple affected relatives: • 2 or more 1st line with diagnosis before age 50 (including the patient) • 3 or more 1st line
Multiple primary cancers in the patient, particularly if breast and ovarian
Male breast cancer
Pathological features: • Medullary or pseudo-medullary breast cancer • Triple negative breast cancer (especially before age 50)
Ashkenazi Jewish descent or other founder mutation ethnic group
Known BRCA1/2 mutation in 1st or 2nd degree relative
Breast cancer and family history of any of the following cancers: • Prostate, thyroid, sarcoma, endometrial, adrenocortical, brain or pancreatic.

Source / Adapted from (Schwartz et al., 2008)

The UK National Institute for Health and Clinical Excellence (NICE) 2006 guidance for the care of women with familial breast cancer stated that “genetic testing is appropriate for only a small proportion of women from high risk families” (pg 7) (NICE, 2006). The Scottish Intercollegiate Guidelines Network publication ‘Treatment for Primary Breast Cancer’ recommends that high risk patients be referred to a genetics service (SIGN, 2013). There is no current guidance for

genetic testing in patients with a family history of breast cancer and a current diagnosis of breast cancer.

Recently published NICE guidelines for Familial Breast Cancer (NICE, 2013b) demonstrate an increased acceptance of the role for genetic testing for women with a family history of breast cancer:

- the threshold for genetic testing for familial breast cancer reduced from 20 to 10 % risk estimation
- women who have been given a diagnosis of breast cancer within the past month and who have a family history of breast cancer, may be offered immediate ('fast track', 'rapid' or ‘early’) genetic testing as part of a research trial (NICE, 2013b).

However current UK guidelines do not provide recommendations for testing at the time of diagnosis out-with the remit of clinical research. This may relate to local genetic laboratory or genetic counsellor service provision or to the current cost / payment structure within the NHS. The provision of testing via clinical research removes the responsibility from local NHS organisations.

In response to publication of the draft 2013 NICE guideline the Scottish Genetics Laboratory Consortium extended their threshold for BRCA testing, this change meant that the risk estimation level to trigger genetic testing fell from 20 per cent to 10 per cent however this guidance has yet to be incorporated into a SIGN publication. In the UK, genetic testing can now be performed for individuals at high-risk of carrying BRCA1/2 mutations (NICE, 2013b).

While the NICE Guideline reduced the testing threshold it recommends that research is required, to provide evidence-based practice, for rapid testing at the time of diagnosis. Genetic testing at diagnosis is now performed faster than before and results can be available before treatment is commenced (Schwartz et al., 2004, Wevers et al., 2011b, Meiser et al., 2008, Trainer et al., 2010a). A BRCA1/2 mutation may alter treatment plans on account of the increased risk of breast cancer recurrence, tumour grade and biological receptor status (Trainer et al., 2010a, Ardern-Jones et al., 2005, Couch et al., 2014, Smith and Isaacs, 2011)[18] .

In 2006, the UK national guidelines did not provide specific guidance for the treatment of hereditary or BRCA-related breast cancer (NICE, 2006, SIGN, 2005). By 2007 risk-reducing strategies for patients at risk of developing breast cancer (including recurrence) took into account 'state-of-the-art' genetic testing that had been identified and agreed by international groups, though at the time the strategies were largely non-evidence based (Schwartz et al., 2008).

Current UK clinical guidelines detail diagnostic and treatment pathways based on tumour and but not BRCA characteristics (SIGN, 2013, NICE, 2013b, NICE, 2013a, NICE, 2013c)[19]. BRCA-related breast cancer treatment options are provided in Appendix E.

[18] An overview of the characteristics of a BRCA-related breast cancer is provided in Appendix C.

[19] Breast cancer treatment information is provided in Appendix D.

5.4 Why Do Women Seek Breast Cancer Related Genetic Information?

There are known differences in the reasons for women attending cancer genetics services. Women attending for predictive genetic counselling and testing do so to establish their own risk. Women with a cancer diagnosis attend cancer genetics clinics to learn of the reason/s that they have cancer and to help improve the chances for family members by knowing their risk for developing cancer (Julian-Reynier et al., 1998).

Distinct reasons for seeking information are supported by the authors of a study that reports different risk perception between cancer survivors and unaffected HBOC family members (Mellon et al., 2008). Unaffected relatives have a higher perception of cancer risk, while survivors have more cancer worries. Factors impacting cancer risk perception and cancer worry are detailed in Figure 5.

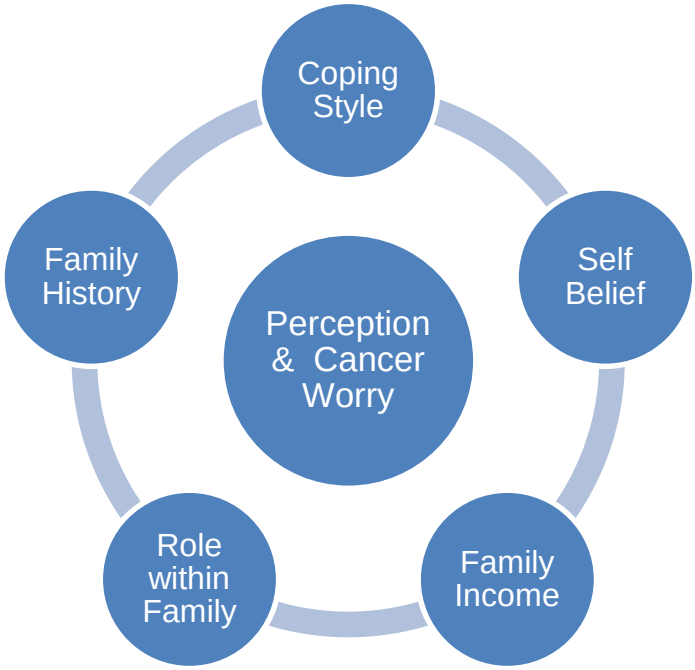
Responsibility is significant in both obtaining information and decision making in regard of cancer-specific genetic information. A Canadian qualitative study (Etchegary et al., 2009) reports that seeking genetic risk information is experienced by most as a responsibility. The authors present 3 dimensions of genetic responsibility:

- for self
- for others
- to assist others to know.

Each dimension carries implications for test decisions: family relationships, family members' desire to know (or not) and to take action (or not) with respect to their own

genetic risk. A series of studies conducted by a team from The Netherlands report similar reasons, or dimensions of genetic responsibility, for patients seeking cancer genetic-specific information however the work offers an alternative focus, rapid genetic counselling and testing. They report that the key reasons for women undertaking genetic testing are to establish knowledge about future cancer risks and choice of preventative surgery, for their increased cancer risk (Wevers et al., 2014).

Figure 5: Perception & Cancer Worry



Source / Adapted from (Mellon et al., 2008)

Is Coping Style a Factor?

Coping style theory is based upon early behavioural theory; Bowens Theory (Bowen, 1978). Within this, Differentiation of Self is a process that enables individuals to separate emotion and thought. When faced with a challenging situation, for example cancer diagnosis or genetic testing, a range of techniques such as information seeking or avoidance will be used to reduce anxiety (Bartle-Haring et al., 2008).

Coping style will influence whether an individual seeks genetic information and how, after testing, they respond. Two main coping styles have been identified in relation to cancer screening and management:

- monitoring or information seeking
- blunting or avoiding (Miller, 1995).

Information seeking is characterised by addressing threatening information. These individuals typically have high levels of worry and anxiety regarding their cancer risk however they will be knowledgeable about their health situation. Patients who adopt an information seeking style require high levels of psychosocial support however it is worth noting that these individuals are more inclined to take a passive role in decision making, deferring to competent individuals such as their doctor. Conversely individuals who adopt an avoiding coping style do not seek information, and they will be satisfied with the minimal amount of information however they will tend to adopt an active role in decision making. Patients who use avoidance techniques generally report low stress levels however because of this they are often given more information because they appear to cope well.

A study, conducted in the UK, that used the previously described GRACE tool (Phelps et al., 2010) to explore patient coping during cancer genetic testing, identified that patients use a range of coping styles throughout the process (Bennett et al., 2012). Furthermore the authors report that the majority of participants are not consistent in their coping response and use a variety of approaches. While they report that a minority of individuals, who lack flexibility and consistently, use a limited or more fixed range of coping strategies.

Coping style and reaction to genetic testing has been explored in a genetic testing study that explores the experience of patients with hereditary colorectal cancer (Shiloh et al., 2008). This publication reports that regardless of coping style participants were interested in genetic testing to inform risk reduction and disease treatment. More recent work recommends that genetic information should presented in an individualised manner that targets the individuals coping style (Vig and Wang, 2012).

Genetic Information to Maximise Survival?

A study by Wevers et al (Wevers et al., 2012b) cites 15 reasons, reported by 26 women who had received rapid genetic counselling and testing, for seeking this information at the time of diagnosis. The most frequently stated reason (73%) is to obtain certainty about the risk of getting breast cancer again, this is followed by (69%) the desire to take preventative action for the unaffected breast and (50%) to choose surgical treatment of the affected breast. These reasons can be viewed as maximising survival.

A recently published study (Jeffers et al., 2014) explored the motivation of women with hereditary breast and ovarian cancer for undertaking BRCA1/2 gene testing. The publication describes “Maximising Survival”, a theme that is common from testing until 2 years after the test. While the study focused its exploration on understanding the experiences of women who receive BRCA1/2 positive results, the survival theme is relevant for a broader population who undertake genetic testing. An American study published in 1994 explored the attitudes of patients with a first degree relative who had breast cancer to genetic testing; 75% reported that they would definitely want to receive genetic testing for BRCA1 when a suitable test was available (Lerman et al., 1994). Reasons that the women reported for wanting genetic information are: to learn about their children’s risks (76%), to increase use of screening (71%), to be reassured (70%), to inform or assist with childbearing decisions (48%) and to adopt healthy lifestyle behaviours (50%). This study did not relate to post-diagnosis testing though it did support the results of a later survey (Andrykowski et al., 1997) that a high uptake of genetic testing should be anticipated within the population who have a family history of breast cancer.

5.5 Psychological Impact of Breast Cancer Genetic Testing

Expectations & Waiting for Results

The Lerman study (Lerman et al., 1994) reported patients’ expectations about the impact of BRCA test results. A positive BRCA1/2 result was anticipated to leave 80% expecting to feel depressed and 77% very anxious, 32% expected a positive result to negatively impact their quality of life and 1 of the 121 participants reported that she would consider suicide. For negative BRCA1/2 test results participants

expected to feel less anxious (83%), 83% expected this to improve their quality of life, 82% would feel more in control, feel less depressed (68%) however 45% would still worry and 25% would feel guilty. However studies report that individuals who receive results of uncertain significance experience prolonged uncertainty and confusion (Culver et al., 2013).

The uptake of genetic testing is variable and there are many reasons for declining testing. In one study that examined the barriers to participating in genetic counselling and testing during breast cancer treatment (Schlich-Bakker et al., 2007) participants who declined, genetic counselling and testing or withdrew early in the process (22%), did so because they do not consider the test to be relevant for themselves. Participants who reported anxiety, about the impact of the result on their health or future health decisions (14%), declined to proceed or postpone testing after the genetic pedigree completion (genetic family tree). A further 7% stopped the process before receiving results because they feared the genetic test result and / or a relative objected. The publication stated that distress, HBOC knowledge, prior genetic testing (in family members) and perceived cancer risk were not reasons for declining the offer of BRCA gene mutation testing or withdrawal from genetic counselling and testing.

Notably these authors state that 81% of the participants supported testing during breast cancer treatment or would prefer an earlier offer for gene testing. They conclude by stating that patients who decline or withdraw from the genetic counselling and testing process would benefit from tailored health and risk education to facilitate their making an informed decision (Schlich-Bakker et al., 2007).

Insecurity concerning genetic status is a common psychological stress whilst awaiting genetic results (Bennett et al., 2012). The period whilst waiting for results is associated with extreme stress; the stress predominately relates to thoughts about personal destiny (Valverde, 2006). In an attempt to minimise this fear-related psychological trauma techniques such as bargaining can be used by the individual (Valverde, 2006). Bargaining involves the individual making assurances, for example 'if I do not have a BRCA1/2 gene mutation I will take more exercise'. Health related behaviour is commonly used within bargaining when faced with insecurity and psychological stress. However Lerman et al (2002) report, little evidence for genetic testing promoting changes in health or risk-reducing behaviours (Lerman et al., 2002). Self-help coping interventions prove useful in reducing anxiety and avoidance behaviour, whilst waiting for genetic test results (Phelps et al., 2013, Bennett et al., 2007).

Does Testing Increase Distress?

A literature review conducted in the last 10 years concluded that genetic testing does not increase psychological distress in breast cancer patients (Schlich-Bakker et al., 2006). However the authors report that, the diagnosis of breast cancer adds to cancer-specific distress before genetic counselling and after genetic test results. Clinicians are advised to be sensitive, to a possible increase in general and cancer-specific distress, following a recent diagnosis.

Later work, conducted by a Dutch research team, reported that the 102 participants in their prospective study of breast cancer patients approached for BRCA genetic

counselling and testing, at the start of radiotherapy, did not experience additional short-term psychological distress (Schlich-Bakker et al., 2007).

However other studies report conflicting results. One study reported that approximately a quarter of patients who undertake predictive testing for BRCA1/2 gene mutations experience cancer related worry (Watson et al., 2004). For women who test positive, worry and mental health issues are at their highest 1 month after receiving the test result, and younger women (<50 years) experience the highest level of worry at this time (Watson et al., 2004).

Participants in the Audrain study (Audrain et al., 1997), who reported the high levels of general distress in response to BRCA1/2 genetic testing were less likely to be married, more pessimistic and described feeling a lack of control over developing breast cancer. Similarly women with the most cancer-specific distress were younger, non-white and also reported low control over developing breast cancer. Correspondingly this study advises that interventions are implemented, to reduce the moderate levels of general and cancer-specific distress experienced by women with HBOC who self-refer for genetic counselling and BRCA gene testing (Audrain et al., 1997).

A follow-on study of long-term impacts, conducted by the Watson team, reported that 40% of the female BRCA1/2 carriers had difficulties with life and / or health insurance. Distress was no different for BRCA1/2 carriers and non-carriers 3 years after the genetic test however a number of non-carriers, albeit a minority, despite

recommendations were not engaged in breast cancer screening programmes (Foster et al., 2007).

Significant levels of psychological distress that range from anxiety to depression are described in response to BRCA genetic testing. These symptoms can be prompted by the testing process (Tercyak et al., 2001) or by family history experiences of breast cancer. This team recommend that, psychosocial support forms an integral part of genetic counselling for all women undergoing BRCA1/2 testing.

More recently authors recommend, that psychological support measures are employed for patients aged below 50 years (Watson et al., 2004). Additional counselling is recommended and support may be required throughout the testing process, for certain groups who have been identified as requiring additional psychosocial support: younger patients, single women with little support, those who are less optimistic, patients who use an avoiding coping style, highly distressed individuals and those with low quality of life (Schlich-Bakker et al., 2007).

In response to distress, at the time of genetic counselling and testing initiated close to the time of diagnosis (Wevers et al., 2012a), the uptake of psychosocial counselling is reported for 1/3 of women. Notably more women who tested BRCA1/2 positive, than negative, attended psychosocial counselling provided by a social worker or psychologist. However many of the reasons for the counselling were related to general coping with cancer and were not specific to rapid genetic counselling and testing. Where issues related to genetic testing the most frequently reported reasons for attending counselling are cancer recurrence, risk-reducing

treatments such as prophylactic surgery and body image. Short-term psychosocial distress was reported by half of the participants; increased levels of distress related to genetic testing was identified, significantly this was in addition to the distress associated with their breast cancer diagnosis.

5.6 Psychosocial Impact of Breast Cancer Genetic Testing

Responses to BRCA Gene Testing

The decision to undertake BRCA genetic testing is not always easy. One study explored relationship support and psychological reactions to testing (Manne et al., 2004). The majority of participants discussed the BRCA test decision and results with their partners. Most partners were supportive. However where little or no support was provided greater distress and relationship strain was reported 6 months after receiving BRCA results. The study concluded that partner support is important particularly for women receiving results of uncertain significance.

Genetic test results can have a life-changing affect. Loneliness and isolation are described in response to a breast cancer diagnosis for women with a BRCA1/2 mutation, this international paper reports on Social Separation (Kenen et al., 2006). Proposed reasons for emotional estrangement or pulling away are associated with a philosophical existence dilemma: increased cancer risk associated with genetic mutation may be interpreted as chronic illness or disability. Loss of identity is alternatively proposed as the catalyst for estrangement.

Participants in the Kenen study (2006) report feeling different and a sense of not belonging. The characteristic use of silence or verbal discretion are associated with social separation. Pretending to be attached was used as a tactic in certain public situations to disguise feelings of separation. Within the Kenen (2006) study population cancer diagnosis plays a significant part in loneliness however this is amplified when BRCA1/2 mutation is identified. The knowledge of a genetic mutation added complex feelings of responsibility and a need to make further health / life changing decisions. Participants described feeling 'out-of-sync' with their peers when making decisions such as increased screening or prophylactic surgeries (while their peers discuss social events). The urgency to make significant health and life decisions make these participants feel isolated and that peer's activities and decisions are frivolous or carry less importance. The authors propose that support groups (face-to-face and virtual) are of value for reducing social separation in women with a breast cancer and BRCA mutation diagnosis (Kenen et al., 2006).

Subtle complications that result from BRCA1/2 gene testing as described in a recent publication (Grubs et al., 2014). An individual's response to testing can alter social relationships with family friends, colleagues and clinicians. Genetic test results can influence on self-concept, career, financial and reproductive choices. Notably a positive mutation status can bring about a sense of urgency which alters or speeds up life plans. However for some women this change is not positive and discrimination may lead to unemployment, social isolation and reduced self-esteem.

While the presence of a highly penetrant genetic mutations confers an increased risk for disease, modifiable behaviours can play a role in risk reduction (Boyle, 2012,

Guinan et al., 2013b). The impact upon health behaviours is reported in a study of women who initiated BRCA1/2 testing (Dorval et al., 2008). However the authors conclude that an established high-risk for breast cancer prior to BRCA1/2 testing does not provide sufficient motivation for women to assume healthy lifestyle behaviours including stopping smoking, taking exercise and undertaking breast screening measures, unless they have already had cancer.

It is unclear what modifiable factors have clinical significance for reducing risk in the presence of a highly penetrant BRCA1/2 gene mutation. A recent meta-analysis reviewed 9 modifiable factors in relation to BRCA and breast cancer risk reduction (Friebel et al., 2014). Modifiable factors that were analysed:

- Reproductive elements - age at first live birth, breastfeeding, number of children and exposure to oral contraceptives
- Screening & prophylactic elements - exposure to mammogram and tamoxifen
- Lifestyle elements - exposures to alcohol, coffee and smoking.

Notably a healthy diet and exercise were not included in their analysis.

Within the Friebel (2014) review limited evidence is reported for modification of breast cancer risk in the presence of a highly penetrant BRCA mutation although a probable association exists with late age at first birth. Later age provides a protective effect for BRCA1 mutation carriers while more evidence is required for the BRCA2 population. A possible risk modifying protective association is reported in the presence of a BRCA1 mutation and further evidence is required for BRCA2 for (high) alcohol consumption and breastfeeding. Smoking is associated with increased breast cancer risk for BRCA2 mutation carriers. The authors advise that current data

relating to alcohol and smoking may not be suitable for clinical translation; study limitations include small sample sizes, convenience samples and retrospective assessments. Large prospective randomised trials and clinical risk assessment tools are required, to clearly identify which modifiable factors confer the greatest risk (and benefit) for the high-risk BRCA population, to provide actionable health behaviour information for cancer risk reduction.

While a BRCA1/2 mutation is the fundamental cause for developing breast cancer the effect of modifying lifestyle risk factors such as physical activity, body weight, alcohol and smoking should be discussed in breast cancer genetics counselling session (Albada et al., 2014). An early study identified modifiable lifestyle factors that could reduce breast cancer risk for women with a highly penetrant BRCA gene mutation. High calorie intake, early age of maximum body mass index (BMI), rapid weight gain between 18 and 30 years are all associated with increased breast cancer risk for this population (Nkondjock et al., 2006). A calorie restricted diet is proposed with particular attention to prevent rapid weight gain in young adulthood. Further work by this team recommended a high quality, healthy diet as a preventative strategy for reducing BRCA-associated breast cancer risk (Nkondjock and Ghadirian, 2007). This message is reiterated by an associated research team who additionally propose a diet rich in fruit and vegetable variety to reduce risk for this population (Ghadirian et al., 2009).

Smoking and alcohol exposure are well known modifiable health behaviours that increase risk for many diseases. They may have additional significance within the realm of highly penetrant genetic mutations, confounding risk and in the presence of

disease worsening prognosis. Image 1 highlights a specific challenge for health professionals though the challenge is relevant when considering all lifestyle behaviours that alter risk and prognosis.

Image 1: Challenging Health Behaviours

Source (Marteau and Lerman, 2001)

An early study that identified that smoking may reduce breast cancer risk in BRCA1/2 mutation carriers (Brunet et al., 1998). This controversial finding rapidly became the subject of further discussion and strong advice not to encourage women with a BRCA1/2 mutation to smoke (Baron and Haile, 1998). Indeed a large prospective study followed 426 high risk families over a 5 year period. This study concluded that smoking may increase breast cancer risk particularly in families with the most penetrant BRCA1/2 mutations (Couch et al., 2001).

Alcohol was proposed as a protective factor for women who carry a BRCA1/2 gene mutation (McGuire et al., 2006). However study results on the whole do not support the proposal. The exception being that BRCA2 mutation carriers who consume moderate levels of alcohol may be offered a possible risk reduction. A more recent

case-analysis study has however proposed that alcohol may offer a protective function for BRCA1 mutation carriers (Moorman et al., 2010). Reassuringly the authors do not propose or advise the use of alcohol as a risk reduction measure and advise further research to investigate this controversial finding.

Three large prospective studies are currently recruiting participants and collecting modifiable lifestyle data from women with BRCA1/2 mutations. These studies may provide much needed data on which to base counselling for factors that may improve cancer risks for women with a highly penetrant BRCA mutation (Guinan et al., 2013a, Pasanisi et al., 2014, Pettapiece-Phillips et al., 2015).

Acceptance of a BRCA test result and associated breast cancer risk may take time and support (Valverde, 2006). In a study conducted in the late 1990s (Metcalfe et al., 2000) approximately half of the participants reported negatively impacted relationships, in response to genetic testing that confirmed a positive result (Julian-Reynier et al., 2000).

Survivor guilt can result when a negative BRCA result is received. A report written by a genetic counsellor, after her BRCA gene test revealed a negative result, maintains that survivor guilt is not an adequate description (Valverde, 2006) and that 'identity loss' (pg 462) provides a clearer description for response to a negative genetic test result. After 30 years of worry about developing breast cancer she describes a 2 year period spent redressing her life view, self-identity and health behaviours. The impact of this negative result left Valverde asking 'why me?' and questioning the importance of her life.

Valverde (2006) received a negative result however her sister received a positive genetic test result. Associated with these results is period of readjustment related to the relationship with her sister. Valverde describes coping with an overwhelming feeling loneliness and fear related to being the only one left when the affected members of her family die. For her sister there is hope that her children will have a close aunt to care for them should she die, unlike when Valverde's mothers generation died leaving daughters with no mother or senior female relatives.

Following genetic testing women describe a range of family connectivity, from improved cohesiveness to social isolation (Douglas et al., 2009) that includes emotional separation (or hostility) and feelings of vulnerability, despite having the support of at least one family member. The impact of BRCA testing on family relationships and dynamics is explored in a qualitative study (Douglas et al., 2009). The impact is three-fold:

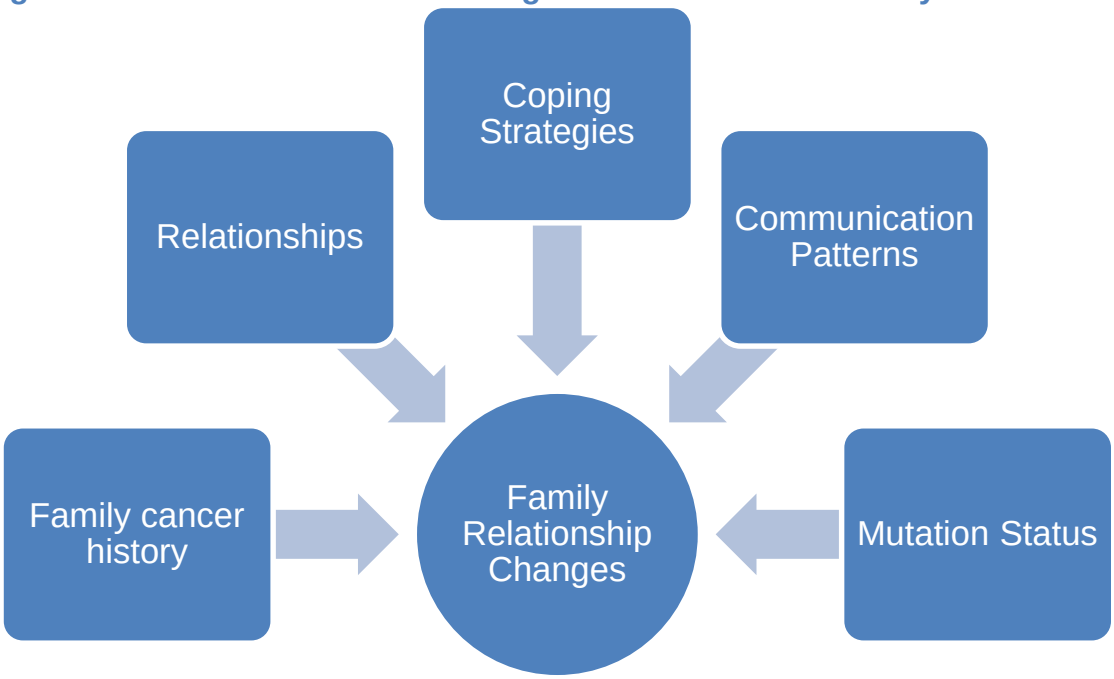
1. A special family role is adopted by the individual tested, this role can be challenging
2. Family discussions change
3. Connections with family members change

Five key factors that influence altered family relationships after genetic testing are shown in Figure 6.

A study published in Psycho-oncology reports that over a third of family relationships are positively affected by genetic testing: families become closer, communication and support improved, appreciation for the relative undertaking testing increases and when results are negative a sense of relief is brought to the whole family (van

Oostrom et al., 2007). Conversely negative effects of the genetic test result in unwanted changes in relationships for approximately one fifth, difficult situations for 13% and conflicts for 4% of the 271 participants.

Figure 6: Reactions to BRCA Testing: Factors that Alter Family Relationships



Source / Adapted from (Douglas et al., 2009)

Reported BRCA1/2 gene testing adverse effects are guilt, enforced secrecy and difficult communication. The authors detail 2 predictors for adverse familial outcomes:

- Disengaged – rigid family functioning
- Enmeshed – chaotic family functioning

Open familial communication should be promoted to ensure optimum disclosure of risk, support and interactions (van Oostrom et al., 2007).

A review published in Ethics in Medical Genetics (Grubs et al., 2014) reports negative changes to social relationships after genetic testing exposes a BRCA1/2 mutation. Women describe emotional un-availability for close family because they are pre-occupied by their genetic status (Metcalfe et al., 2000). In addition the obligation to disclose a BRCA1/2 mutation to family members is often seen as a burdensome.

BRCA Disclosure

The motivation to share BRCA1/2 gene information is multi-factorial. Studies report responsibility for family as a motivator for undertaking BRCA testing (Hallowell et al., 2003, Etchegary et al., 2009, Wevers et al., 2011a). This responsibility can be a source of psychological distress, although sharing genetic information with family members is likely to result in the provision of emotional support (Hughes et al., 2002) that in turn alleviates distress (van Oostrom et al., 2007, Manne et al., 2004). Communal coping is a supportive strategy that aids coping when faced with a shared threat (Lewis et al., 2006).

Additional factors that impact BRCA1/2 gene disclosure are age (of the proband and the relative), relevant cancer diagnosis, the number of daughters in the family and the presence of any cancer related psychological disturbance impacting close relationships. These researchers conclude that the personal and emotional characteristics of the proband impact upon disclosure of BRCA1/2 gene information to family members (Julian-Reynier et al., 2000).

Three roles predominantly adopted by women: maintaining of family relationships, promoting (and sometimes controlling) healthy behaviour and support seeking are discussed within a paper that explores the ethical dilemmas experienced by women who undertook HBOC genetic testing (Foster et al., 2004). When these roles are well established, and strong supportive relationships exist, the communication of difficult genetic information is reported to bring ethical dilemmas that conflict with the care giving responsibility. These tensions create barriers to communication. One example illustrates the participant being selective about which relative they will inform about the genetic risk, giving consideration to age, feelings and the right not to know (Foster et al., 2004).

A large survey-study reported that 97% of participants report their BRCA result to at least one relative, significantly the test result does not influence disclosure (Cheung et al., 2010). Disclosure of HBOC risk is a complex issue for women to face after genetic status and cancer risks are revealed (Forrest et al., 2003, Foster et al., 2004). Ethical dilemmas oppose moral obligations to disclose and protect family members (Clarke et al., 2008).

A French multi-centre study reports disparities of BRCA1/2 gene status disclosure within families. The authors report that siblings are most frequently notified, with sisters (87%) then brothers (79%), followed by mother (71%), children (70%) and father (69%) (Julian-Reynier et al., 2000). Notably, women are more often informed of genetic testing than men despite conveying a risk for male relatives (Julian-Reynier et al., 2000). This may indicate the tested woman perceives the results as

having more value for female relatives or that her relationship with the female relatives resulted in easier communication.

Similar findings have been illustrated by Hallowell (2003) with participants facing a greater burden when considering for example revealing the risk to their brothers. Furthermore sisters are reported to gain support when sharing BRCA1/2 test results with each other (Hughes et al., 2002). When 2 or more sisters are mutation carriers they may benefit from communal coping strategies (Lewis et al., 2006, Koehly et al., 2008). The Koehly (2008) study examined the shared BRCA experience of sisters; reporting that sisters have similar levels of cancer risk perception and cancer worry. These authors report positive association with relatives (sisters) providing support, this results in low levels of anxiety and depression. Sharing and mutual support from a sister/s can facilitate acceptance, coping and adaption following the receipt of information that confirms a highly penetrant genetic mutation (Koehly et al., 2008). Hughes (2002) does however state that emotionally distant relatives may act as a barrier to effective sibling communication and support.

A study of HBOC and family communication reports that adoption, divorce, remarriage, family conflicts and large age difference between siblings can obstruct the processes of obtaining and providing information (Green et al., 1997). A survey study of 1,103 participants from broad ethnic and socio-economic backgrounds explored factors that impact family communication of BRCA test results. The authors report that older age and Asian race are negatively associated with results communication (Cheung et al., 2010). However greater knowledge of HBOC and higher socio-economic status correlate with superior communication of results.

These authors conclude that these predictors are adopted by genetics services to improve family communication of cancer risks, for example where a patient is assessed as having low knowledge of HBOC education. Such assessments should be undertaken with an aim of improving communication within the family.

A study that explored communication of BRCA test results to offspring, following genetic testing, reported 62% of patients informed children aged between 8 and 21 years (Tercyak et al., 2013). However results are more likely to be disclosed when negative or uncertain / uninformative compared with positive results. Children over the age of 13 were more informed than younger children.

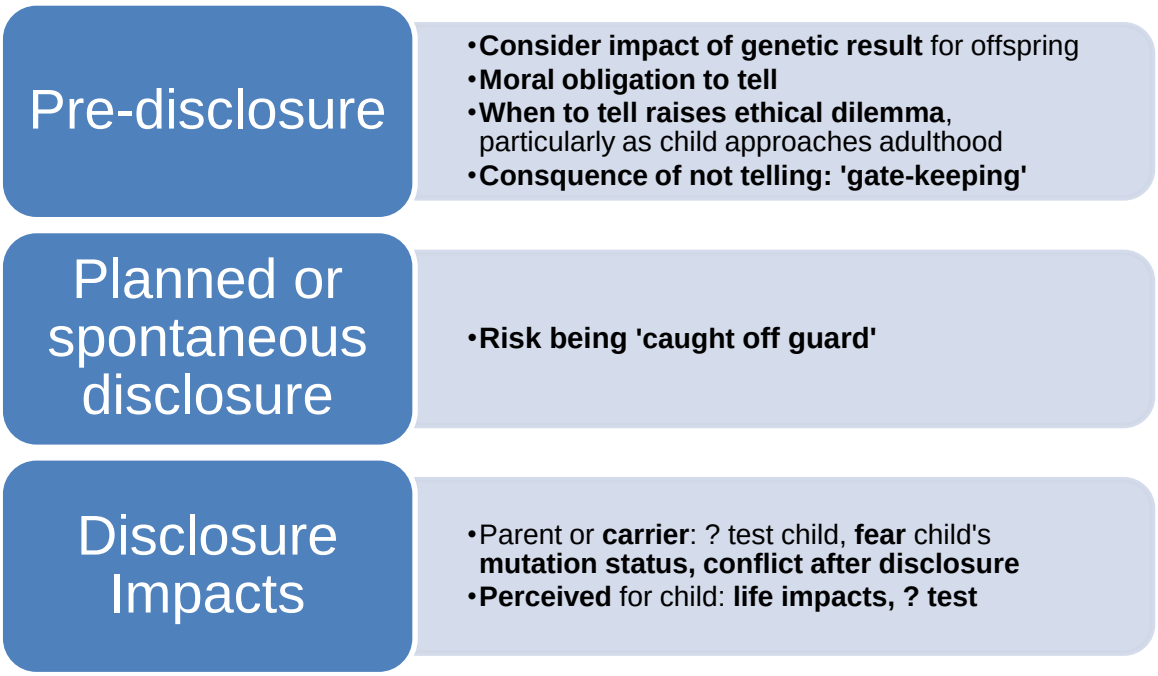
A qualitative interview study reports maternal concern for protecting and educating children about HBOC risk. Most parents participating felt relief and a fulfilled sense of parental duty after telling their children. Age appropriate genetic information is recommended by the parents. Notably an 'immunizing effect of disclosure' (pg 303) was viewed as preparing the child for possible family cancer diagnosis, while parents who chose not to tell were advised to disclose results in the future. Recommendations are made for genetic counsellors to take an active role in advising parents how to deliver genetic information to children (Patenaude et al., 2013).

An earlier study describes 3 phases of disclosure (Clarke et al., 2008), these are displayed in Figure 7. While the study relates to parent and child disclosure it is predicted that similar phases and responses occur with all disclosure. Pre-disclosure the parent considers in relation to her offspring: cancer risk, loss of potential goals, potential genetic discrimination related to finance / insurance and life partner and the

child's emotional responses. Increased poignancy is reported when participants talk about their daughters. Participants report being 'caught off guard' (pg 801) prior to a planned disclosure. For example, genetics was discussed by a 14-year old in relation to a school project however the mother lied when asked about 'bad genes' (pg 801) in the family; the lie was justified as protection.

The possibility that your offspring will carry the BRCA1/2 gene mutation is the greatest fear for parents (Clarke et al., 2008). The psychological impact of this fear and responsibility pre-disclosure creates significant conflict and distress however these lessen after disclosure. The focus changes to supporting the child and whether / when they should undertake BRCA1/2 gene testing.

Figure 7: Phases of Disclosure



Key: relevant text for the broader family relationships are highlighted (**bold**)

Source / Adapted from (Clarke et al., 2008)

6. AIMS & OBJECTIVES

Aims

This project aims to investigate experiences and opinions relating to genetic testing and the impact these have on treatment decisions in women who have a family history of breast cancer and who have undergone genetic testing for the BRCA1/2 genes following diagnosis.

Objectives

- To identify the factors influencing genetic test and breast cancer treatment decisions
- To explore the experiences of genetic testing for women with a family history and subsequent diagnosis of breast cancer
- To evaluate the impact that genetic testing has on breast cancer treatment decisions
- To compare experiences of women tested before and after breast cancer treatment to determine whether the timing of the genetic test impacts the experience
- To identify plausible and acceptable approaches to improving breast cancer patient management following genetic testing.

7. METHODOLOGY

As a qualitative researcher it is essential to acknowledge and define:

- stance and external influences
- theoretical approach, methodologies and philosophies used throughout the research.

7.1 Stance & External Influences

I am graduate nurse with over 20 years of registered practice, I have worked clinically within the National Health Service (NHS) and other healthcare organisations; primarily in the acute hospital settings. However the majority of my career has been spent working in clinical research within the NHS, university and commercial research settings.

This research was not commissioned by any organisation or department. Financial assistance has been obtained from University of Dundee Staff Wavier Scheme, NHS Tayside Breast Endowment Fund, NHS Tayside Clinical Genetics Endowment Fund and the Scottish Research Nurse & Coordinators Network.

Project supervision and research support have been provided by key members of the NHS Tayside Clinical Genetics Department and the Centre for Research into Cancer Prevention and Screening University of Dundee. Input from three highly knowledgeable clinicians and researchers is acknowledged: Dr Jonathan Berg, Professor Annie Anderson, Ms Jacqueline Dunlop.

7.2 Approach

This work broadly takes a Grounded Theory approach (Glaser and Strauss, 1967, Glaser and Strauss, 1999, Strauss and Corbin, 1998) where theory are discovered or emerge from dialogue, topics, categories and themes that exist within the data: Inductive theory development. Grounded Theory research is frequently used within nursing and healthcare research (Dunne, 2011, Gelling, 2011); it is an established methodology for providing insight and understanding of the patient experience (Hernandez, 2010). The use of an accessible methodology, familiar to colleagues (particularly those within the breast care team) was a fundamental factor in selecting this research approach. For this reason Grounded Theory was selected in preference to a generic thematic analysis approach.

Two content analysis approaches, Discourse (Crowe, 2005) and Content analysis (Elo et al., 2014), were considered for this project. Both approaches are ideally suited to conversation and transcription analysis (Silverman, 2000). However because these approaches focus on the use and context of language (within the phenomenon) they were rejected. Furthermore, these approaches are better suited to observational research that is conducted in the environment where the (clinical) interaction occurs.

The use of Interpretive Phenomenological Analysis (Smith et al., 2009, Larkin et al., 2011), an approach ideally suited to understanding the patient experience, was considered. This approach, like Grounded Theory, uses a ‘bottom up’ approach where the researcher develops theory from the data, rather than testing current theory. Similarly, the use of interview and transcription data is applicable to this

approach. While this approach was considered to be more appropriate than the previously described content analysis approaches, Grounded Theory was considered to be more widely accessible to the researcher and clinical colleagues.

An Interpretivist approach (Ormiston et al., 2014a) has been employed with the aim of producing in-depth qualitative data that illustrates the diverse experiences and opinions from the patient group. Relationships between the categories and themes have been evaluated using a constant comparative or substantive approach (Glaser and Holton, 2004). This data analysis approach facilitated the generation of categories and themes that have been explored and refined to develop knowledge (of the patient experience) and theory.

An alternative Positivist approach (Bryman, 2012) was considered; this approach uses existing formal theory to develop or test hypothesis and themes that emerge from data (Polgar and Thomas, 1995, Glaser and Strauss, 1999, Sarantakos, 1998a). At the outset of this study, the patient experience of early BRCA gene testing was unexplored; formal theory was not available to test, correspondingly a Positivist approach was rejected. Furthermore (and significantly), patient\ experiences where neither known nor anticipated. Thus the development of a priori hypothesis[20] and themes (to test) would have relied upon researcher imposed, pre-conceived opinions that could restrict the study scope and (adversely) impact theory development.

[20] A priori hypothesis is based on assumptions and generated before research begins.

Whether a literature review should be undertaken has been the source of much debate by Grounded Theorists (Dunne, 2011) and healthcare researchers (Heath, 2006, McCallin, 2003). In simple terms purists, such as Strauss and Corbin (Strauss and Corbin, 1998), argue against conducting a review of literature which may contaminate data collection and theory development while the more pragmatic, including Glaser, assume "theoretical sensitivity" (p11, section 3.1) (Glaser and Holton, 2004) and propose that a "respectful yet critical stance" (p115) (Dunne, 2011) is adopted.

A wealth of published literature relating to breast cancer and predictive BRCA1/2 genetic testing was available; this provided background theory and knowledge to inform the potential scope of study (Dunne, 2011, McCallin, 2003). To further defend the use of relevant literature, established qualitative researchers recommend a review of existing theory to frame the research question (Creswell, 2003, McCallin, 2003) and prior to developing new concepts and theory (Stern, 2010). Employing a pragmatic, reflective approach permits the researcher to acknowledge and engage with related theory and prior experience whilst developing new concepts (McCallin, 2003); for example the critical use of existing literature can promote creative thought to develop new theory. Since it is particularly suited to a new or emerging field, such as early genetic testing, this pragmatic approach to literature has been adopted.

As previously described, analysis approaches that have been applied are founded within inductive, interpretive and constructive scientific methods (Ormiston et al., 2014b, Bryman, 1988, Blaikie, 2007). This Interpretivist approach creates representations and interpretations from participants' narratives. However

understanding has been taken from the narratives and interpretation of the data and not from related literature or published theory.

Grounded theory proposes that data collection, development of topics and themes continues until saturation; where new data does not present additional meaning. Theoretical Saturation has been adopted and is fundamental to the sampling plan (Carter and Henderson, 2005, Strauss and Corbin, 1998, Bryman, 2012).

Throughout the study (design, documents and thesis) the term ‘opinion’ is used in preference to the term ‘attitude’. An opinion is a point of view or belief, how a person thinks about something; opinion is subjective and based on emotion or an individual’s consideration of fact or an event (OxfordEnglishDictionary). Attitude is a demonstration of opinion or how a person acts in a given situation (OxfordEnglishDictionary). Opinions are more accessible through interview however it is acknowledged that the two are closely related and that attitude may be guided by opinion.

Experience and opinions of BRCA gene testing have been explored with the aim of uncovering the factors that influence uptake of the test and response to test results. Coding topics, analysis categories and sub-categories have been developed by the researcher to assist analysis. The investigation focuses on whether a progression towards BRCA gene testing at the time of diagnosis to inform treatment decisions would be acceptable and feasible.

Where a participant had undertaken early genetic testing their experience has been fully explored. However the majority of participants recruited to the study undertook BRCA genetic testing after diagnosis. In order to investigate opinions relating to early genetic testing participants were asked hypothetically how they would respond to an offer of genetic testing at the time of diagnosis. While this required participants to consider hypothetical situations it was determined that they would base their response on opinions that had been formed during their genetic test and breast cancer experiences.

Throughout the project it has been assumed that an external reality exists independent of peoples beliefs about or understanding of the reality: the Philosophical stance taken is based in Realism (Ormiston et al., 2014b).

In relation to knowledge and how it is acquired or Epistemology (Truncellito) a Pragmatic Inductive stance (Ormiston et al., 2014b, Glaser and Strauss, 1999, Ritchie and Spencer, 1994) has been adopted: individuals gather evidence from experiences then build knowledge based on the evidence. Furthermore this epistemologic stance acknowledges that the participant's and researcher's prior experiences and knowledge cloud their judgement and the researcher's analysis (Ormiston et al., 2014b). This research is concerned with experiences and knowledge; it is acknowledged that the participants' narrative of their experience and knowledge are therefore clouded. Facts, values and opinions will cloud experience or knowledge. Additionally, time will play a role in clouding the experience or knowledge; it has been assumed that where the experience occurred more recently the participant will have better recall of the event and their emotional response to the

event. It is recognised that recall bias may occur, particularly where participants undertook genetic testing experience some time ago. However in defence, this exploratory study aims to illustrate a broad patient experience, furthermore a rich narrative, indicating good recall, was provided by all participants.

Theories of truth have been considered: Coherence and Correspondence Theories of Truth (Dowden and Swartz, Ormiston et al., 2014b) have been adopted. The Coherence Theory of Truth relies on an account or narrative being supported by more than one additional account for verification; where a participant has provided alternative statements that support an account or opinion the account has been adopted as true. Additionally where a narrative or statement is supported by another independent account, for example by another participant's narrative, the account has been adopted as true; Correspondence of Truth (Ormiston et al., 2014b).

Inconsistencies and contradictions exist within the narratives, where these occur the Pragmatic Theory of Truth has been adopted; it has been assumed that the participant believes the statement to be true because it is useful or helpful to them. To assist synthesis, during analysis, generalisations have been made where categories and themes recur. Where generalisations have occurred, either throughout one or several narratives, effort has been made to illustrate theory using dialogue from each participant with the aim of providing equal voice to all participants. Proportional participant representation has been attempted throughout the presentation of study findings. However the small sample size has inevitably lead to greater representation for some participants.

Validity and Reliability

The researcher's objective perspective and reflections are woven throughout the analysis although true representations of the participants' narrative have been retained as the principal method for communicating the constructed topics, categories, themes and theory. Furthermore this technique, exemplified by the use of verbatim quotations, has been adopted to enhance internal reliability and validity with the central aim of minimising researcher bias.

Additional techniques have been employed to reduce researcher effects and improve internal validity, reliability and objectivity (Sarantakos, 1998b, Silverman, 2000):

1. A neutral and professional stance has been adopted when engaging with participants with the aim of creating an interactive, non-judgemental relationship between myself (the researcher) and the participants. This neutral position has been maintained throughout the research, in order to produce objective findings. For study participants, and the audience, the purpose of the research has been clearly presented. Furthermore my status as nurse and researcher has been revealed with the aim of communicating professional biases and values. For (potential) participants, this was detailed in the invitation letter and participant information sheet, additionally participants were advised during the informed consent discussion prior to consent and enrolment. Neutrality assisted candid discussion of the genetic test patient experience; had the research been conducted by a member of the clinical genetics team this neutrality may not have been achieved.
2. Throughout the study, during data collection and analysis, a reflective and reflexive stance (Sarantakos, 1998b) has been adopted with the aim of

moderating potential researcher bias (Ormiston et al., 2014b) and providing flexibility to the data collection. However adherence to the interview schedule (Appendix G) has occurred primarily to reduce researcher bias. Comprehensive verbatim transcriptions that include subtle utterances, and reflective research notes have been produced by the researcher, close to the time of interviews. This complete written record of interviews ensured accurate representation of participant narratives; this is fundamental in reducing researcher bias. Furthermore these transcriptions and high quality audio files are source data from which summary data matrices have been created. Reflective notes, also taken during analysis, are clearly identified and distinct from participant dialogue. The use of reflective notes assisted researcher objectivity and thematic development.

3. As a novice qualitative researcher the use of supportive (anonymised) discussions, following interviews, with member/s of the clinical genetics team acted as debrief sessions and assisted the reflective process. Additionally study progress meetings with experienced researchers and members of the clinical team occurred predominantly during analysis; thematic development was assisted by these study findings discussions.

Sharing interview recordings and transcriptions with participants was identified as a method to increase validity. Participants were advised that copies of their data were available. However no participant requested to receive the interview transcription or audio file therefore it was deemed that this technique could offer little benefit to the project. For this technique to prove valuable participants would be required to read and / or listen to their data, then confirm accuracy. However participants did request

results from the study; a lay report will be produced although this is not intended to increase study reliability or validity.

7.3 Research Design

Following a review of qualitative and quantitative methodologies, qualitative methodology was identified as the most suitable method for investigating patient experience. Quantitative methodology was rejected because it was anticipated that the patient experience data would be broad ranging and that numeric coding techniques would be inadequate for capturing meaning.

A detailed assessment of qualitative methodologies was conducted to identify an appropriate approach to explore patient experience and opinion. This evaluation focused on four methodologies: questionnaire, focus groups, semi-structured and in-depth interviews. Particular consideration was given to the study population and the potentially sensitive issues that relate to the patient experience. The advantages and disadvantages of the methodologies examined are detailed in Appendix F / Table 15: Qualitative Methodologies - Advantages & Disadvantages.

In-depth interviews were judged to be the most appropriate methodology because they would yield rich data that would illustrate the diverse experiences and range of opinions of this patient group. Semi-structured and structured interview methodologies were rejected; they were considered less applicable to the investigative nature of the study. Fixed questions and / or pre-determined ordering of the interview schedule would reduce reflexivity to adapt the interview schedule (Sarantakos, 1998b) to the participant narrative; impacting data depth and quality.

In-depth interview methodology is particularly applicable for exploring sensitive topics, such as the issues that surround breast cancer and genetic testing. Furthermore a Grounded Theory approach combined with interview methodology (Hernandez, 2010) is most appropriate to inquiry that seeks to understand opinions, motivations, decisions and the impact of decisions (Lewis and Nicholls, 2014). Additionally in-depth interview methodology is suitable for a small number of participants: it was anticipated that study population would not exceed 20.

A mixed methodologies design, combining questionnaires and in-depth interviews, was evaluated with the aim of collecting a large amount of scoping data prior to conducting in-depth interviews that would yield richly descriptive data from a smaller number of participants[21]. However the use of questionnaires was rejected primarily because they would not capture sufficient detail to facilitate understanding of the patient experience or opinion. Furthermore, available open-code (free to use) validated questionnaire tools relevant to this field of enquiry could not be identified, further excluding the use of questionnaires. The process of developing a validated questionnaire that could gather useful qualitative patient experience data, to address the study aims was considered to be out-with the study scope and timescale. Significantly the pilot or validation process would require peer and patient input; early genetic testing is a new phenomenon, correspondingly the researcher and Clinical Genetics colleagues judged the engagement of hereditary breast cancer patients or breast care colleagues to be inappropriate.

[21] Study proposal approved by sponsor and submitted to Tayside Committee for Medical Research Ethics (Ref: 11/ES/0045). Favourable ethical opinion was not received.

While exploring mixed methodologies focus groups were considered, as an alternative to questionnaire methodology, with a comparable aim of scoping data in advance of conducting in-depth interviews. Focus groups function as a group interview; the researcher initiates questioning then participants interact, discussing the topic, while the researcher facilitates and observes (Polgar and Thomas, 1995). Focus groups could have been used to collect general genetic testing patient experience data, prior to conducting in-depth interviews (ideally with the same participants) to yield the personal opinion (and / or potentially sensitive) data. Focus group methodology is popular within healthcare research however it was rejected primarily for issues of data collection; accurate recording would require sensitive (and potentially expensive) equipment that was not readily available to the researcher. Furthermore, as a novice researcher, it is important acknowledge limitations; the role of focus group facilitator was judged to exceed my skill and experience. In-depth interviews were subsequently retained however mixed methodology research, utilising questionnaire or focus group methods, was rejected.

Formal qualitative research training was undertaken by the researcher following protocol development, Sponsor approval, submissions for Research Ethics and NHS permissions and prior to conducting any interviews[22]. As a result of undertaking qualitative research training, reflexivity was identified as an essential element for the success of the project (Koch and Harrington, 1998). The study protocol had been

[22] The courses attended were run by the Social Research Association and Liz Spencer who is known for her role in developing the Framework Approach.
Additionally, informal training was undertaken and focused on the following:

- Reading; In-depth Interview theory and techniques
- Listening to anonymized interview recordings
- Reading anonymized interview transcripts
- Discussions and interview technique practice sessions (including reflective note taking) with experienced qualitative researchers.

submitted and approved prior to completion of this research training. However had this training identified potential issues or conflicts relating to the choice of in-depth interview methodology, this would have been reconsidered; this did not occur. Furthermore the extra knowledge acquired during training reinforced the decision and choice of In-depth interview methodology.

In-depth interviews explored key topics:

- knowledge of genetic testing
- views on timing for genetic testing following a breast cancer diagnosis
- impact of test results on treatment choices.

For sampling and recruitment purposes the study population has been divided into three test result subgroups and two timing categories. While it has been anticipated that equal distribution (between the groups and categories) would not be reached, the study aimed to sample participants from each.

A qualitative approach has been used throughout. Reflexivity to adapt the interview schedule (Appendix G) to fit the participant's experience is vital for sensitive and appropriate data collection. This reflexivity permitted the researcher to add topics that were revealed during another participant's interview and / or topical events to the discussion, for example when a celebrity received genetic testing for the BRCA gene this could be discussed in relation to the participant's experience.

In-depth interviews were audio recorded[23]. Interview recordings have been used to compile a comprehensive verbatim record or transcription of the interview, soon after the interview had been conducted. Supplementary reflective notes were taken by the researcher following interview and transcription.

In-depth interviews had been conducted with a similar population, and using the same interview schedule, during an earlier NHS Tayside Department of Clinical Genetics investigation. This earlier work, conducted in 2009-10 by Richard Watson (BMSc) and Jonathan Berg (East of Scotland REC Ref: 09/S1402/25) is acknowledged as a catalyst for developing this work. As detailed in Silverman (Silverman, 2000) secondary data analysis makes use of previously produced relevant data. Relevant permissions were sought and obtained prior to accessing the previously generated anonymised interview data to supplement the interview data collected during this current research.

Ritchie and Ormiston (2014) state the appropriateness of previously produced data and its use within the scope of the new research requires careful consideration. The value of this previously generated data is unquestionable: it provided data from the group of patients with confirmed BRCA gene mutations and reduced the number of new interviews that were required. Notably the offer and uptake of genetic testing close to diagnosis remains uncommon, furthermore the identification of a BRCA

[23] Recording and verbatim transcribing of the interviews took place only with explicit written informed consent. The digital audio recording device was located close to the researcher and participant. The participant was advised that the device would be turned on at the start of the interview, this occurred after the informed consent discussion and confirmation that the participant was happy to start the interview. Participants were free to stop the interview at any time, additionally they were free to refuse to discuss any item without affecting their relationship with the researcher or any current or future care.

mutation after breast cancer diagnosis affects only a small number of patients within NHS Tayside. Therefore it was important to make use of all potential participants and data. Ethically it was considered to be more appropriate to make use of previously generated valuable data than to contact these participants for a second interview.

A review of the interview schedule that had been used in the previous interviews occurred. The schedule was confirmed to be appropriate and relevant to the aims of this study. Subsequently, it was determined that the same interview schedule would be adopted for the new study, for consistency and to ensure comparable data. The (previous) schedule had been developed by the NHS Tayside Clinical Genetics Team.

Regrettably only 5 of the original 16 interviews contained complete audio data, furthermore the associated transcripts were incomplete. Consequently, these recordings were used to complete the 5 previously generated transcriptions, providing comprehensive verbatim transcripts for use in secondary data analysis. These 5 interviews were of exceptional value and contributed all the data for participants with a confirmed BRCA1/2 mutation. The remaining 11 interview recordings were lost and only transcripts existed; the accuracy and quality of the transcripts could not be checked (Ritchie and Ormiston, 2014) therefore these would only be used if after 20 interviews saturation of themes did not occur.

7.4 Sample Design

The research population have been selected to in order to explore the research questions:

- What are the experiences of genetic testing, for mutations in the BRCA1/2 genes, for women with a diagnosis and family history of breast cancer?
- What is the impact of testing for a BRCA1/2 gene mutation before or during breast cancer treatment compared with testing after treatment from the perspective of women with a diagnosis and family history of breast cancer?

The research team included a NHS Tayside Clinical Genetic Counsellor. A role undertaken by this individual was to facilitate participant recruitment; identifying potential participants from the NHS Tayside Clinical Genetics Department database. Prior to performing this delegated role the Genetic Counsellor was trained according to the study sampling plan and eligibility criteria.

Primary Research Question

The primary aim has been to explore diverse patient experience and opinions following breast cancer diagnosis and BRCA1/2 genetic testing. For recruitment, interviewing (data collection) and analysis purposes the population has been divided by gene test result into 3 sub-groups:

- Identified mutation in BRCA1/2 genes
- Detected no mutation in BRCA1/2 genes
- Detected BRCA1/2 variant of uncertain significance.

Standardised recruitment, matching the characteristics or number of participants in the three sub-groups, was not planned or attempted. The researcher was informed,

by the Genetic Counsellor, of the participant's BRCA1/2 status prior to conducting the interview. This knowledge was deemed necessary, to facilitate sensitive exploration of the participant's response to the genetic test result.

In 2012 the NHS Tayside Clinical Genetics Department had a potential group of 32 participants with an identified BRCA1/2 mutation. However the previously conducted study (09/S1401/25) had invited 29 and recruited 16 of this potential 32 participants. The sampling plan included the use of supplementary anonymised interview data from the previously conducted 2010 study (09/S1401/25)[24]. The 3 remaining potential participants with BRCA1/2 gene mutation had undertaken gene testing since 2011. These and any newly identified (by NHS Tayside Clinical Genetics Department) eligible patients during this study would be invited to participate.

It was proposed that a minimum of 10 anonymised interviews (09/S1401/25), transcriptions and supporting data would be required for analysis; this would continue until no new themes emerged or theoretical saturation is reached. However only 5 complete recordings and transcripts were available; these would be added to the data set for analysis.

In 2012 the NHS Tayside Clinical Genetics Department had a potential group of around one hundred patients with breast cancer who underwent BRCA1/2 gene

[24] Consideration was given to inviting these 16 participants to take part in this study. However following discussions with the East of Scotland Research Ethics Service, it was determined that it would be ethically appropriate to maximize the use of the valuable anonymised data and not to invite the women to take part in a similar study. Additionally the remaining 13 who had not responded to or declined the invitation (and reminder) for the previous study were considered for invitation to this study however it was deemed unethical to contact them with a similar study. Additionally it would be highly likely that these patients would decline or not respond to an invitation to this study.

analysis during the preceding ten years with results that identified no BRCA1/2 gene mutation or BRCA1/2 variant of uncertain significance. These and any newly identified eligible patients (during this study) would be invited to participate. It was however anticipated that a number of the potential patients would not be eligible as would no longer be living in Tayside and some would have died.

Secondary Research Question

The secondary research question aimed to explore experiences and opinions relating to the time that the genetic test was undertaken. To answer the second research question Purposive Sampling has been employed. Potential participants were selected for comparison based on the time that gene testing occurred:

- Category A: tested after breast cancer treatment
- Category B: tested before or during breast cancer treatment.

As for the primary question, no attempt was made to standardise recruitment by category. The researcher was informed by the Clinical Genetics Counsellor of the test timing category prior to conducting the interview.

Knowledge of the patient experience and impact of testing for the BRCA1/2 gene, from the perspective of patients from each Category, was identified as fundamental to understanding (and improving) the patient experience and breast cancer outcome. At the outset, it was acknowledged that equal distribution between these Categories could not be achieved. The majority of patients with breast cancer who undertook gene testing (at the time of this research) did so after cancer treatment (Category A). This reflected clinical practice. In 2012 the NHS Tayside Clinical Genetics patient population had an approximate ratio of 10:1 (Category A:B).

A recruitment strategy was implemented that aimed to create a sample that was more equally distributed between the Categories. Recruitment would be biased towards patients tested before or during breast cancer treatment (Category B) to ensure that data would be available to illustrate and represent the experiences and opinions from these patients (Category B). Additionally this recruitment strategy would ensure that all eligible NHS Tayside Clinical Genetics patients who had gene testing before or during breast cancer treatment (Category B) were sampled / invited to participate. This sub-population would be similar to those patients who, it is anticipated in the near future, may benefit from early BRCA1/2 gene analysis at the time of breast cancer diagnosis to inform their treatment choices (Wevers et al., 2014).

At the outset of this study the potential population, having results that identified no BRCA1/2 gene mutation or a BRCA1/2 variant of uncertain significance, are:

- Category A: up to 90 participants
- Category B: up to 8 participants.

Sampling aimed to contact participants in equal numbers from Category A and B until all Category B potential participants had been contacted, thereafter potential participants were contacted from Category A. Additionally patients with the most recently conducted genetic test would be contacted first. It was proposed that a minimum of 10 new interviews be conducted and analysed. Ongoing analysis and data collection occurred until theoretical saturation was reached.

A major limitation in the previous study (09/S1401/25) is that of the 16 participants with an identified BRCA1/2 gene mutation; 15 fit Category A and 1 fits Category B.

In 2012 clinical practice had changed (since 2009-10) and a small group of patients had received genetic testing around the time of breast cancer diagnosis (Category B); these new potential participants were invited to participate. Additionally the Clinical Genetics team alerted the research team if / when any new potential participants were identified. Genetic testing at the time of breast cancer diagnosis was carried out more frequently in 2012 than in 2009 however was (and is still) relatively uncommon.

Eligible participants

Eligibility criteria are detailed in Figure 8. Potential participants had a diagnosis and family history of breast cancer. These patients have a significantly increased risk of carrying a BRCA1/2 gene mutation (Malone et al., 1998, Chappuis et al., 1999).

All participants in the population had undergone gene analysis for the BRCA1/2 gene. The study sample corresponds with the high-risk population who it is anticipated that in the near future will benefit from early BRCA1/2 gene analysis at the time of breast cancer diagnosis to inform their treatment choices (Wevers et al., 2014).

Figure 8: Eligibility

Eligibility Criteria	Female
	With a family history of breast cancer
	Have / have had a breast cancer diagnosis
	Received HBOC Counselling by NHS Tayside Clincial Genetics
	Have undergone BRCA1/2 analysis
	Willing to give consent & participate in the study
	Currently live in Tayside

In Tayside women with a family history of breast cancer commonly attend the Family History Breast Cancer Clinic (FHBCC), receiving annual review and screening for breast cancer. However it was anticipated that the study population would include women who had not known their family history at the outset. For these women, family history is established after breast cancer diagnosis, often in response to age of diagnosis and / or tumour characteristics. However family history may be identified in response ambiguous breast and / or ovarian cancer histories[25]. In such cases, where high risk genetic family history is suspected, clinical and genetic investigation can confirm HBOC diagnosis. Including these women in the population was considered essential, this phenomenon is not uncommon and the experience and impact of genetic testing for this population is different from those who receive routine reviews via the NHS Tayside Family History Breast Screening Clinic.

[25] Ovarian cancer increases the risk for developing breast cancer CLAUS, E. B., SCHILDKRAUT, J. M., THOMPSON, W. D. & RISCH, N. J. 1996. The genetic attributable risk of breast and ovarian cancer. *Cancer,* 77**,** 2318.

Exploring the perspective from these women would add alternative and equally valid experience and opinions[26].

Secondary data analysis of anonymised and complete data from the previous research (Ref: 09/S1402/25) supplemented the interviews conducted in this research. Eligibility for the previous research required gene analysis before or during breast cancer treatment that identified BRCA1/2 gene mutation.

Potential participants would be selected from a Convenience Sample of approximately 135 eligible patients who were under the care of NHS Tayside Clinical Genetics Department. Theoretical Sampling, an ongoing process, would stop when:

Theoretical Saturation occurred (Carter and Henderson, 2005, Strauss and Corbin, 1998)

OR

20 interviews had been conducted, transcribed and analysed

AND / OR

16 previous study (09/S1401/25) anonymised interviews had been analysed.

The previous study (09/S1402/25) population did not include patients who had undergone BRCA1/2 gene analysis with results of no BRCA1/2 gene detected or variation of uncertain significance. This population have been included in this research and sampling has targeted patients who received BRCA gene testing after

[26] Women who had received gene testing but did not have a breast cancer diagnosis were not included in the study population. It was determined that the experience of these women would have differed from the population with a breast cancer diagnosis. While women with no breast cancer experience similar gene testing processes the impact of the result will not be the same, i.e. decision making does not involve breast cancer treatment choices.

2000. Furthermore the previous study had invited all women with an identified a BRCA1/2 mutation who had undertaken BRCA testing prior to 2010[27]. Therefore sampling targeted patients with an identified BRCA1/2 gene mutation, who undertook testing after 2010.

The sampling plan proposed that potential participants from the NHS Tayside Clinical Genetics eligible population were contacted with an invite to participate and where possible this would be sent close to the time that their genetic test was conducted. It was predicted that this would have a positive effect on recruitment: where genetic testing was a recent event potential participants may be more willing to participate additionally it was anticipated that recall of events would be greater.

7.5 Setting

The study has been conducted in an NHS Scotland location: NHS Tayside where approximately 300 new breast cancer diagnosis are made per year (NHSTayside, 2009). In NHS Tayside breast cancer can be diagnosed at one of three clinics:

- Family History Breast Cancer Clinic
- One Stop Breast Clinic
- Scottish Breast Screening Program Clinic[28].

While most women were diagnosed by the Family History Clinic not all women were aware of their family history at the time of their diagnosis[29]; in such cases family history was identified shortly after diagnosis.

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[27] Recruitment for the previous research took place in 2009 and concluded in 2010.
[28] The patient's diagnostic experience will vary depending on which clinic the woman has presented at however the procedures, investigations and standards of care will be the same across the three clinics.
[29] Diagnosis occurred at the One Stop or Screening Program Clinic.

All patients diagnosed with breast cancer by NHS Tayside are cared for by a multi-disciplinary team (MDT); clinicians and health care professionals are responsible from first referral to diagnosis, treatment planning and ongoing patient care. The MDT comprises of Breast Specialist Doctors (including surgeons, medics, radiologists, pathologists, oncologists and geneticists), breast care nurses, genetic counsellors and radiographers. The MDT format is common across breast care facilities within NHS Trusts in the UK and similar teams exist abroad[30]. Within the NHS Tayside MDT one breast surgeon has specific responsibility for family history patients and close liaison with the Clinical Genetics Department; the role of this one surgeon is noteworthy and may not be replicated across other NHS Trusts.

7.6 Recruitment

Required approvals were obtained prior to commencing recruitment / patient activities see Table 5 for details**.**

Table 5: Approvals Summary

Organisation	**Role & Reference**	**Approved**
University of Dundee & NHS Tayside	Sponsor Ref: 2012GE01	March 2012
Tayside Committee for Medical Research Ethics Committee REC 1	Ethics Ref: 12/ES/0038	June 2012
NHS Tayside	R&D Ref: 2102GE01	June 2012

[30] The stimulus for implementing the MDT in the UK was as a result of the NHS Breast Screening Programme in 1998. Initial up take was slow however Department of Health guidance for improving clinical for breast cancer in 1996 TAYLOR, C., MUNRO, A. J., GLYNNE-JONES, R., GRIFFITH, C., TREVATT, P., RICHARDS, M. & RAMIREZ, A. J. 2010. Multidisciplinary team working in cancer: what is the evidence? *BMJ (Clinical Research Ed.),* 340**,** c951-c951. This saw a notable increase in the acceptance and uptake of the MDT format for teams and improved working practice relating to breast cancer care.

It was anticipated that recruitment would be completed within 12 months, by end of June 2013. In-line with recruitment in the previous study we anticipated that 50% of participants contacted would be recruited. Potential participants have been be contacted in blocks of 10. To reduce potential drop-outs the researcher aimed for a short period of time, up to 8 weeks, between first contact and recruitment (completed interview). It was predicted that a minimum of 10 and a maximum of 20 participants would be recruited.

Potential participants were identified and contacted by NHS Tayside Clinical Genetics Department with a postal Invitation Letter, Reply Slip and Participant Information Sheet (Appendices H, I & K). Participant documents were created with input from the NHS Tayside Breast Support Group: Perth Branch. Throughout the recruitment period the NHS Tayside Clinical Genetics Counsellor, who was a member of the research team, conducted ongoing clinical / patient database searches for eligible potential participants. Prior to closing recruitment the NHS Tayside Clinical Genetics Counsellor ran a final search of the clinical database to ensure that no potential participants had been omitted; confirming that all potential participants had received an invitation to participate.

Participants received written and verbal study information. The Participant Information Sheet (PIS) was provided by post and at the interview session. Verbal information was provided when a potential participant wished to discuss the study (prior to arranging an interview) and / or when the participant was contacted to

arrange the interview and again at the interview prior to obtaining written informed consent[31].

Each participant was given every opportunity to clarify any points they did not understand and, if necessary, more information provided where required. Participants were given a minimum of 24 hours to consider the information provided. It was emphasised that the participant may withdraw their consent at any time and without loss of benefits to which they otherwise would be entitled. The Informed Consent Form (ICF) (Appendix L) was provided and completed at the arranged interview session. Informed consent was obtained by the Principal Investigator (PI) prior to conducting any protocol specific procedure. The PI is an experienced researcher with current Good Clinical Practice (GCP) and informed consent training. The PI and the participant signed and dated the ICF to confirm that consent had been obtained. In line with local procedures the participant retained one original ICF, the other original was filed in the Clinical Genetics Patient Record and copy stored in the Investigator Site File.

Specific consent has been obtained to:

- conduct audio recording of the interview
- use anonymised quotes
- collect clinical information from medical records.

Optional consent has been obtained for the use of:

- audio recorded interview, transcription and data in future research

[31] The verbal explanation of the study covered all the elements specified in the PIS and ICF.

- 3-4 digits of postcode for deprivation score calculation[32].

Participants were advised that they could / can inform a member of the research team or Clinical Genetics team at any time should they wish to have their interview recording and / or transcription and / or supporting clinical data to be destroyed. Destruction would / will be recorded on Enrolment Log. To date no participants have withdrawn.

7.7 Ethical Issues & Measures Taken

At the time of this study all participants were under the care of the NHS Tayside Clinical Genetics Team. The clinical team conducted a study eligibility and clinical appropriateness check prior to sending invitations. No invitations were sent to patients who had recently received an unconnected clinical diagnosis.

Perceived risks for participants were minor although did include possible distress. To minimise this participants were informed that the interview would explore topics relating to breast cancer and genetic testing.

Informed consent was sought through the provision of a Participant Information Sheet (PIS) and detailed discussion relating to study participation. The PIS was provided by post, thereafter a reply slip was returned by post and follow-up telephone contact with those who express an interest in taking part. Completion of

[32] Discussion with the Ethics Committee specified that only the first 3-4 postcode digits could be collected. However deprivation score calculation requires a full postcode therefore this was not carried out SCOTTISHGOVERNMENT 2012b. Scottish Index of Multiple Deprivations. Edinburgh.

written informed consent took place prior to conducting the interview. Participants provided specific consent for the interview being recorded using digital audio equipment. The researcher obtaining informed consent recently undertook Good Clinical Practice and is experienced in obtaining informed consent for research. The TASC Informed Consent SOP was followed.

Interview discussions included participant thoughts and feelings, based on their experiences of genetic testing following the diagnosis of breast cancer. It was anticipated that topics such as coping with cancer diagnosis, fears (such as pain, death, etc.), body image, sexuality, relationships, lifestyle and financial aspects could be discussed. Participants were invited to express their views but were informed that they did not have to discuss or reveal anything that they were uncomfortable with. Furthermore participants were informed that the researcher is a registered nurse. Interviews were conducted in a private room. Participants were advised that the interview could be stopped at any time.

The research team included genetic counsellors who were / are available should participants wish to discuss anything further. NHS Tayside Clinical Genetics Department operates an open access policy for further appointments and advice. Participants were reminded of this policy at the time of informed consent.

Had a participant revealed a medical issue to the researcher or had the researcher considered that a participant had a medical issue this would be discussed with them at an appropriate time (either during or at the end of the interview). Furthermore the patient would be advised to seek advice from their General Practitioner or relevant

Health Care Professional (for example their Breast Care Nurse). Clinical oversight was provided by the Chief Investigator and the NHS Tayside Clinical Genetics Department.

Participants were advised that while there may be no direct benefit to their participation, the findings may inform more research and / or may change the way that genetic services are provided in the future. The process of talking about an experience that evokes emotion may have cathartic effects. While this effect was not anticipated a beneficial effect was reported by a number of participants who stated that they had previously not considered or talked about their genetic testing experience in such depth.

Where possible invitations to participate were be sent close to the time that a potential participant's genetic test was conducted. It was predicted that this would have a positive effect on recruitment: where genetic testing was a recent event potential participants may be more willing to participate additionally it was anticipated that recall of events would be greater.

Participation was entirely voluntary and did not affect any medical care received at the time of participation or in the future. In order to minimise inconvenience interviews were scheduled at a time and place that suited the participant. Interviews were conducted in a private room with only the researcher and participant (and close relative if desired) present.

All Investigators and study site staff involved with this study comply with the requirement of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and uphold the Act's core principles. Information about and gained from participants has been treated in confidence and will remain confidential. Only named and delegated researchers have access to this information for research purposes. All study data, paper and electronic, will be stored and archived by NHS Tayside for 5 years thereafter they will be destroyed. The TASC archiving SOP will be followed.

Computers used to collate and store the data have limited access measures via user names and passwords and are subject to backup. Computers are located in a locked office in the Clinical Genetics Department on a password protected secure NHS or University of Dundee computer system. Where laptops are used no patient identifiable data is used or stored. Table 6 summarises data storage systems that are in use.

Study data are anonymised; to maintain participant confidentiality they contain no participant name or patient identifiers:

- Participants are identified by a two digit study number
- Anonymised data is identified by a two digit study number (as per the previous study) and prefixed by the letter 'R'.

Published results will not contain any personal data that could allow identification of individual participants.

Table 6: Data Storage

	Paper Site File	Word Document	Excel Spreadsheet	Digital File
Invitation Log	X n=1	X n=1		
Participant Log	X n=1	X n=1		
Identifiable Information Log	X n=1		X n=1	
Interview Recording				X n=17
Transcription	X n=17	X n=17		
Highlighted Transcription	X n=17	X n=17		
Data Familiarisation			X n=1	
Topics		X n=1	X n=1	
BRCA Test Analysis Categories			X n=1	

Electronic and paper records containing participant's personal identifiable data are held confidentially and securely in the NHS Tayside Department of Clinical Genetics. Personal identifiable data is stored separately from the study data on the Identifiable Information log. This log contains each participant name, address, telephone number, NHS Tayside Clinical Genetics identifier and two digit participant number. Additional anonymised recruitment logs provide the following:

- Invitation log = anonymised record of study contacts / potential participants
- Participant log = anonymised record of recruited study participants.

Permissions may be requested / obtained from the Chief Investigator for use of the anonymised digital interview recordings, transcriptions and supporting clinical data for secondary data analysis.

The majority of interviews (10/12) were conducted in a TASC clinical research facility (CRF). The remaining 2 interviews were conducted at the participant's home. The protocol and relevant NHS Tayside Procedures were followed.

No incentives or reimbursements were available, participants were informed of this via the PIS. Free parking was available and provided for interview appointments conducted at NHS Tayside facilities.

If any participant believes that they have been harmed in any way by taking part in this study, they have the right to pursue a complaint and seek any resulting compensation through the University of Dundee and NHS Tayside, the research sponsor. Additionally, as a patient of the NHS, they have the right to pursue a complaint through the usual NHS process. The NHS has no legal liability for non-negligent harm. However, if a participant is harmed and this is due to someone's negligence, they have grounds for a legal action against NHS Tayside but they may have to pay their own legal costs. No physical pain or changes to lifestyle were anticipated. No complaints or harm have been reported.

7.8 Data Collection

Recruitment, interviews and early analysis have been conducted concurrently.

August 2012 – March 2013

Date collection commenced in August 2012. The initial assessment for Saturation of Themes took place late February 2013, as scheduled and following the completion of

10 interviews and interview transcripts[33]. By March 2013 it was identified that saturation had been reached for eight coding topics[34] for the sub-group / category of participant: test after breast cancer treatment / identified no mutation in BRCA1/2 genes. Nine participants had been recruited (see Table 7 – shaded blue). Furthermore saturation for a significant proportion of the sub-themes had been reached for this sub-group/category. No further potential participants for this sub-group / category were contacted after March 2013 although one additional participant was subsequently recruited, this followed a February 2013 invitation to participate.

Table 7: Participants & Targeted Recruitment Plan March 2013

	Test (by Category) Totals	Participants with identified mutation in BRCA1/2 genes	Participants with detected no mutation in BRCA1/2 genes	Participants with detected BRCA1/2 variant of uncertain significance
Test Result Totals (by Sub-group)	**16 (11 + 5)**	**5**	**10**	**1**
Tested after breast cancer treatment (Category A)	**12 (9 + 3)**	**3**	**9**	**0**
Tested before or during breast cancer treatment (Category B)	**4 (2 + 2)**	**2**	**1**	**1**

Table Code: **Participants** **Anonymised data**

Recruitment Plan	Further Participants Required	No Further Participants Required

[33] The tenth participant was recruited in November 2012, complete interview transcription and data familiarisation for this participant's data occurred by February 2013.

[34] The eight coding topics were later developed into the four key themes:

- Genetic Testing
- Impact of Test and Results
- Early Genetic Testing
- Hereditary Cancer.

March 2013 – August 2013

For the remaining 5 sub-groups / categories saturation of themes had not been reached by March 2013 (Table 7: Participants & Targeted Recruitment Plan March 2013 – shaded grey) therefore additional participants were invited / recruited from those sub-groups and categories[35]. Targeted recruitment continued from March until August 2013. However no potential participants were available[36]. In addition the previous study (09/S1401/25) did not provide further anonymised data.

Early Analysis

Data familiarisation, identification of common topics / data categories and assessment for saturation of themes occurred prior to conducting in-depth analysis; this provided flexibility to adapt interview topics should new subjects, previously not considered, become apparent and recruitment[37].

Anonymous interviews, transcriptions, supporting clinical data and reflective notes have been examined using structured qualitative analysis methods for emerging

[35] Participants with:

- no mutation detected in the BRCA1/2 genes tested before or during breast cancer treatment
- identified a mutation in the BRCA1/2 genes: both before or during breast cancer treatment
- detected BRCA1/2 variant of uncertain significance: both before or during breast cancer treatment.

[36] i.e. no patients underwent genetic testing before or during cancer treatment (whose test identified mutation, no mutation or variant of uncertain significance in BRCA1/2 genes) and no patients underwent gene testing after cancer treatment with an identified BRCA1/2 mutation or BRCA1/2 variant of uncertain significance.

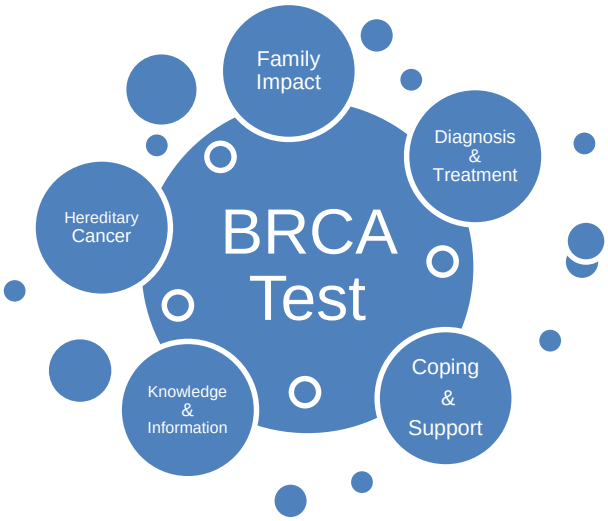
[37] Recruitment would continue until theoretical saturation of themes occurred OR 20 participants had been recruited. Assessment for saturation occurred after 10 participants have been recruited, interviews conducted, transcribed and early data analysis had been completed; thereafter assessment for theoretical saturation was ongoing. Where complete data saturation was reached recruitment would stop.

themes. Secondary data (09/S1401/25) has been analysed in the same way as the new data.

Supplementary reflective notes were taken by the researcher following interviews, during transcription and throughout data familiarisation. These notes add the researcher's perspective and assisted the development of thematic analysis categories.

Data familiarisation involved focused listening to interview recordings, reading transcriptions and reviewing clinical data. During this early process eight common coding topics were identified: BRCA Test, Family Impact, Diagnosis & Treatment, Hereditary Cancer, Information, Knowledge, Coping and Support. These inter-related coding topics are represented in Figure 9.

Figure 9: Data Coding Topics



For the purpose of this representation the following coding topics have been combined:

- Knowledge & Information
- Coping & Support.

Within the data these topics are independent.
Within the data Diagnosis & Treatment is a combined theme.

Appendices M and O provide extracts from coded interview transcriptions and supporting clinical data and the BRCA Test coding matrix.

The final interview was completed in May 2013, with 12 participants enrolled and 5 anonymised sets of data (interview, transcript and clinical data) obtained. Table 8, details recruitment by sub-group and category[38]. Saturation of themes was reached for one sub-group / category (previously described). While the four key themes are represented saturation of themes was not reached, within the study timeframe, for the remaining five sub-groups / categories: participants from the detected BRCA1/2 mutation and variant of uncertain significance sub-groups and tested before or during breast cancer treatment.

Table 8: Final Recruitment

	Test (by Category) Totals	Participants with identified mutation in BRCA1/2 genes	Participants with detected no mutation in BRCA1/2 genes	Participants with detected BRCA1/2 variant of uncertain significance
Test Result Totals (by Sub-group)	**12** / **5**	**5**	**11**	**1**
Tested after breast cancer treatment (Category A)	**10** / **3**	**3**	**10**	**0**
Tested before or during breast cancer treatment (Category B)	**2** / **3**	**2**	**1**	**1**

Table Code: **Participants** Anonymised data

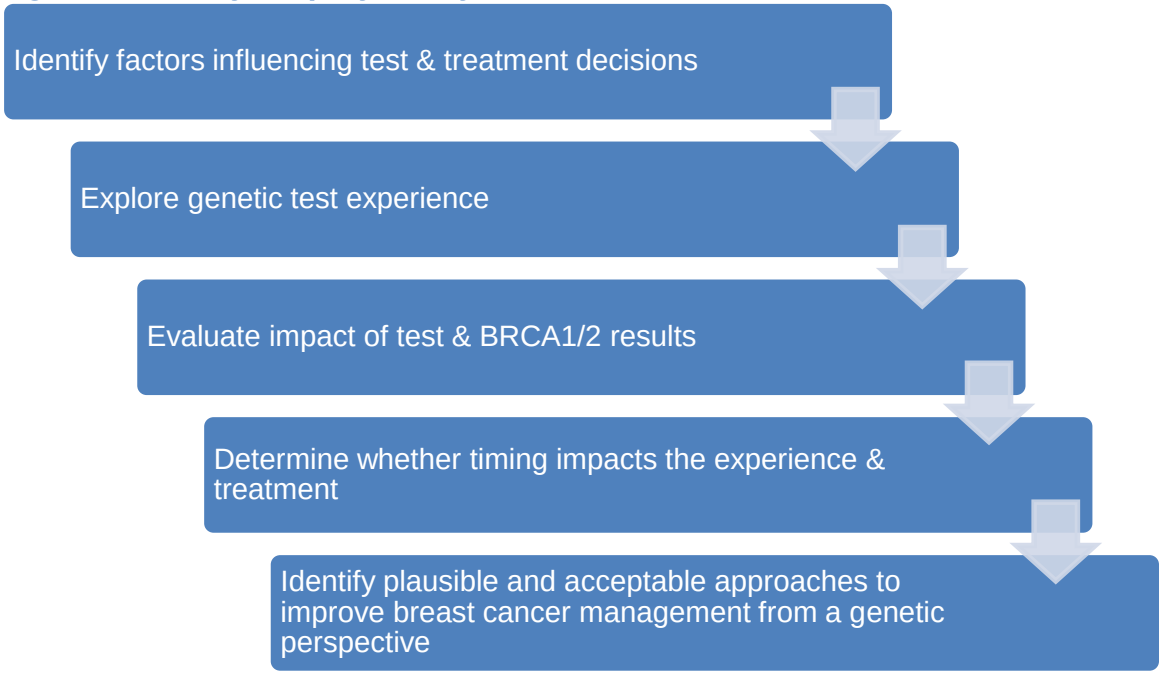
The End of Study Declaration was submitted to Sponsor, REC and NHS Tayside in August 2013.

[38] Ten participants underwent genetic testing after breast cancer treatment all with the result of no mutation detected in BRCA1/2 genes. Two participants were tested before or during cancer treatment, one with the gene test detecting no mutation in BRCA1/2 gene and one with the test detecting BRCA1/2 variant of uncertain significance.

7.9 Data Interrogation & Analysis Approach

The primary aim of this study has been to provide structured in-depth qualitative analysis of interview, transcription, supporting clinical and reflective data to investigate experiences and opinions, of women with a diagnosis and family history of breast cancer who undertook genetic testing for mutations in the BRCA1/2 gene, in order to answer the research questions. Figure 10 details the systematic data enquiry process that has been used in attempt to realise the aims of the study.

Figure 10: Study Enquiry & Objectives



The study data and anonymised data from the previous study (09/S1401/25) have been combined into a single dataset. Anonymous interviews, transcriptions, supporting clinical data and reflective notes have been examined for emerging themes. A substantive approach has been taken: the data provides a window onto the participant's world.

Secondary data obtained from the previously conducted study has been combined with the new data with the aim of expanding the findings from the previous study and to expose new viewpoints / themes. During analysis no distinction has been made between data source.

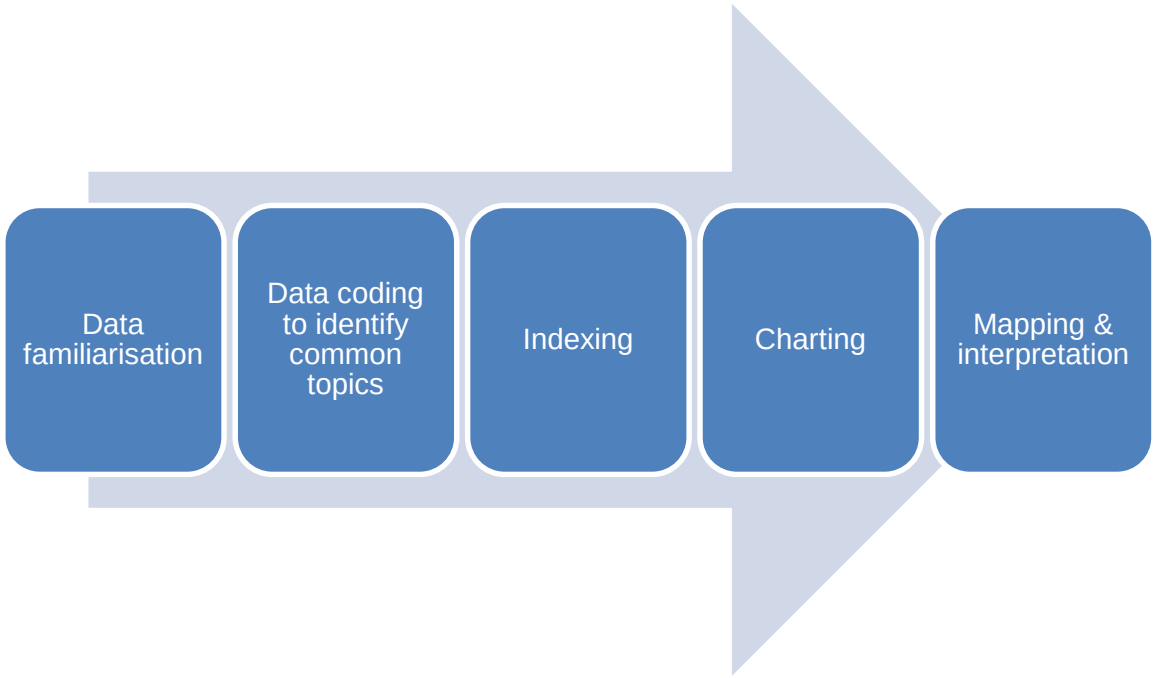
Systematic in-depth qualitative analysis has been on-going, analytical and investigative. Furthermore the data analysis process started close to conclusion of the interview when reflective notes were taken. Thereafter data familiarisation commenced with detailed listening (to interview recording), reading (of interview transcriptions) and reflective note taking. The process of transcribing the interview and creating coded transcriptions further underpinned data familiarisation and early analysis. An interpretative framework has been adopted to provide understanding based on the participant's experience and perspective relating to Genetic Testing and Breast Cancer. Throughout analysis themes have been developed to provide knowledge of the patient experience of genetic testing for the purpose of informing breast cancer treatment.

The Framework Approach has been utilized to summarise the data and assist synthesis using common topics and categories (identified early in analysis) and sub-categories (developed later in the analysis process)[39]. Data summaries, that retain their links to the participant, are key elements and benefits of implementing the Framework Approach (Ritchie and Spencer, 1994, Ritchie et al., 2014, Spencer et al., 2014)[40] [41].

[39] An extract from a coded transcriptions are presented in Appendix M.
[40] Appendix N provides extracts from a Coded Interview and the BRCA Test Theme Word Document.
[41] Appendix O provides an extract from the BRCA TEST Coding Matrix

Data management, or the process of making qualitative data manageable, required considerable sorting and labelling (Spencer et al., 2014). Throughout the study, manual data management and coding methods were used (Ritchie and Spencer, 1994)[42]. Figure 11 details the 5 stages of data analysis.

Figure 11: Data Analysis Process



Source / adapted from (Ritchie and Spencer, 1994)

[42] Consideration was given to the use of Computer Assisted Qualitative Analysis (CAQDAS) programs however following detailed enquiry that focused on 4 CAQDAS programs (NVivo8, MAXqda, ATLAS6 & DRS) and discussions with experienced qualitative researchers CAQDAS was considered to have limited use in this study. Training time and cost to purchase a relevant CAQDAS program were the rationale that prohibited the use of this type of tool.

A key to successful manual data management is familiarity with the data: during the familiarisation process the investigator immersed herself in interview dialogue, transcription text and clinical data. Following data familiarisation and early data analysis, colour codes were allocated to denote each of the common topics:

Grey = BRCA Test	Yellow = Diagnosis & Treatment	
Red = Hereditary Cancer	Green = Family Impact	Purple = Coping
Pink = Support	Dark Blue = Knowledge	Blue = Information

Transcription statements / text of interest were subsequently highlighted and colour-coded according to these 8 common topics, creating Highlighted Transcriptions [43] (Appendix M and N). Where dialogue related to one or more Topic the text block has been highlighted using all relevant colour codes[44]. Highlighted, coded dialogue relevant to the BRCA Test topic was transferred, to the following documents which have been used to assist data analysis:

- Microsoft Word documents, for each of these 8 topics. These contains all text relevant to the topic, sub-divided by participant (Appendix N)
- Microsoft Excel Topics spreadsheet
- Microsoft Excel BRCA Test Topic spreadsheet (Appendix O).

[43] Highlighted transcriptions are stored electronically as Microsoft Word documents.

[44] For example, Participant 12 dialogue:

when somebody tells you that it is a genetic thing, that is the first thing that you think of, you know is it going to affect the rest of my family I don't think it is, I think you just deal with it.

Spreadsheets contain text extracts; quotes taken from transcripts and investigator comments/reflective notes. These spreadsheets[45] have been used to create thematic matrices to:

- Summarise data to assist data management
- Identify common topics
- Identify analytic categories and sub-categories to assist data synthesis, whilst ensuring that data retain their links to the participant.

Reflexive and reflective structured in-depth qualitative analysis has been carried out to investigate patient experience and opinions relating to the BRCA test. Analysis required:

- In-depth interview recordings
- Comprehensive interview transcripts
- Supplementary:
  - Reflective notes of the interview, transcription and data familiarisation experience to enhance interview / transcription data
  - Clinical data
- Thematic Matrices (Ritchie and Spencer, 1994, Spencer et al., 2014) (Appendix O) .

This study investigated dialogue that has been coded to the BRCA Test topic; detailed qualitative analysis focused on this topic. However where a coding topic (Figure 9: Data Coding Topics, see page 114) related to or closely impacted opinions

[45] Password protected to prevent unintended edits.

relating to the BRCA Test (or treatment choice) the associated dialogue was included in BRCA Test thematic analysis[46].

Inductive and deductive, cross-sectional and non-cross-sectional analysis methods have been used:

- Cross-sectional analysis where data are comparable
- Non cross-sectional analysis where data are not comparable[47]

A bottom-up, inductive approach has been the primary analysis method. Synthesis of thematically sorted verbatim data and summaries, using the Framework Approach, has generated concepts and themes. This is a new area with little published research; early and interim literature reviews revealed no early genetic test theory. However relevant predictive genetic test and breast cancer theories are acknowledged and have been utilised in deductive analysis; these theory has been applied (in the later stages of analysis) to corroborate inductively developed themes. Furthermore the literature review conducted after thematic development identified new early genetic test theory; correspondingly this was applied deductively to test and confirm inductively developed themes. Where possible topics, categories and themes have been given the name or words that the participant/s used.

As described previously (Sample Design, Section 7.4) the first assessment for Saturation of Themes occurred at a scheduled time-point: following the recruitment

[46] Although the majority of dialogue from these additional coding topics was not explored within the scope of the study, for example while diagnosis and treatment were identified topics, the investigation did not seek to explore these specific topics unless an experience or opinion related specifically to genetic testing or impacted choices relating to genetic testing.

[47] For example: To investigate whether there is a different experience and opinion that relates to the timing of the genetic test, data from Category A and Category B have been firstly analysed using cross-sectional analysis then meta-level cross-sectional analysis has been carried out, where unique cases are revealed non-cross sectional analysis has been employed.

of 10 participants and completion of interview and transcriptions (including early data familiarisation). This assessment to identify new (and recurring) themes took a pragmatic, informal approach. Predominantly within each coding topic two or three dominant responses occurred, although less commonly up to five have been identified. Where no new themes have been identified, in the presence of data rich with recurring themes, this has been assessed as a Saturation of Themes[48].

Saturation occurred for participants from the largest sub group / category but due to the small sample size it has been assumed that this has not been reached for the remaining 5 sub-groups / categories for each of the 8 coding topics. The ongoing assessment did identify new responses within the data, therefore saturation has not been reached within the study timeframe. However rich data from the small representation of participants from 4 sub-groups / categories is provided. Recruitment and ongoing assessment for Saturation occurred until recruitment closed, after the 11 month recruitment period.

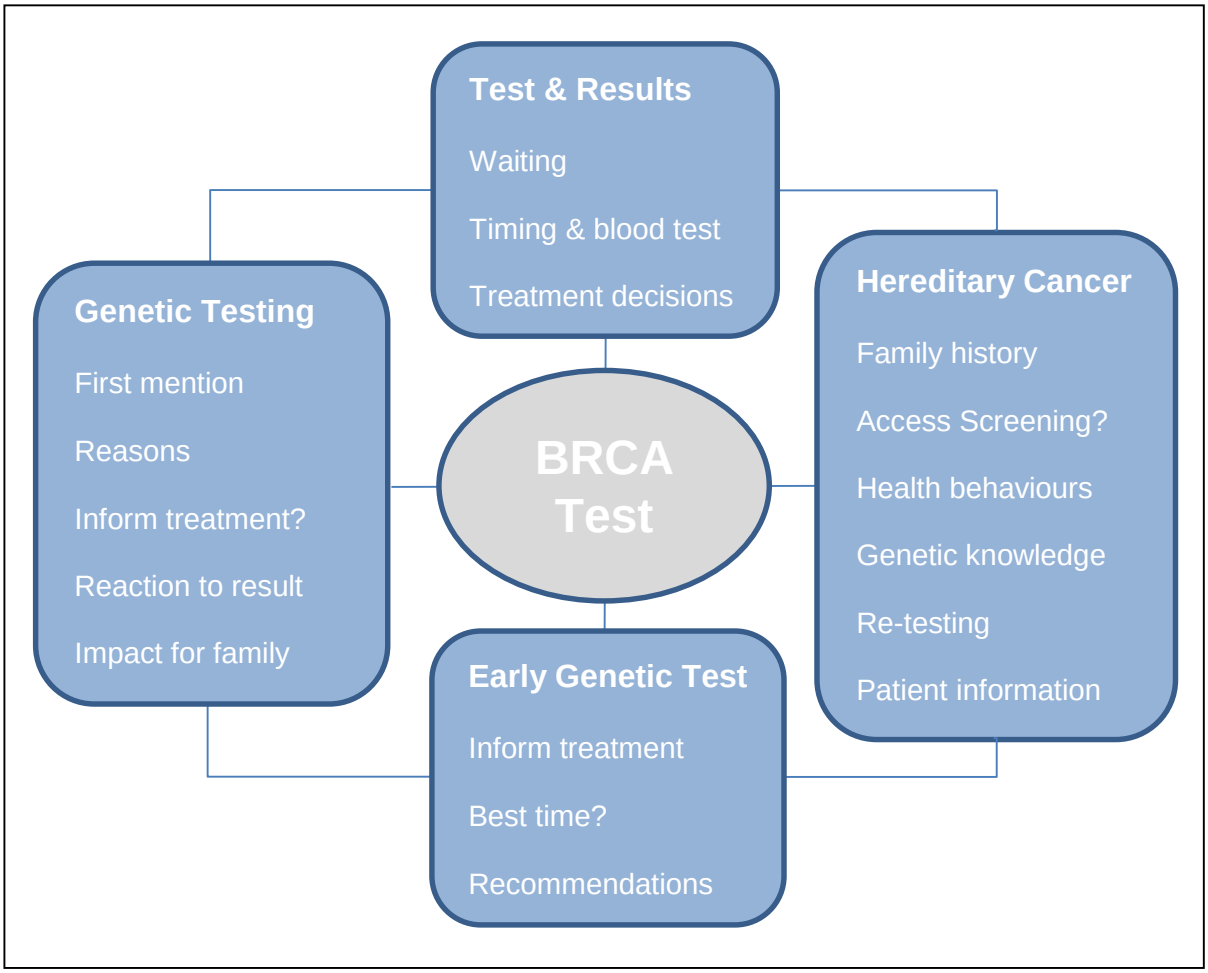
Infrequently, data inconsistencies have been identified, and have occurred in response to a hypothetical question or less commonly as a result of poor recall. Triangulation methods (Denzin and Lincoln, 2005, Lewis et al., 2012, Silverman, 2000) have been used to explore and interpret these differing perspectives; contradictory narratives have been explored, to confirm meaning. For example, where a participant contradicted themselves, triangulation has been employed to conduct detailed inquiry. This involved checking each relevant statement against the

[48] For example: the primary reason that participants cite for undertaking the test was either for themselves or their family. At the time of the initial assessment these 2 distinct responses were equally represented by participants regardless of the timing or result of their test. Saturation of this analytic sub-category was established.

other. Where a consistent or dominant opinion is revealed, this has been interpreted in favour of the contradictory opinion. However where no dominant opinion is identified the participant's uncertainty has been represented.

The BRCA Test topic data has been organised using 4 analytic categories and 17 associated sub-categories. These categories and sub-categories have been developed from the data then utilised to assist systematic data synthesis. Verbatim transcription data from each interview has been sorted and summarised using the analysis categories and sub-categories then scrutinised to further develop themes, the use of audio interview data assisted the analysis process. While the data has been summarised for the purpose of synthesis ready access to the source data has been retained. Themes have been further refined during the writing of this report. Details of thematic analysis categories and sub-categories associated with the BRCA Test Topic are shown in Figure 12: BRCA Test Topic, Analytic Categories & Sub-Categories. Dialogue relating to each analytic sub-category is not present in every interview (nor was it anticipated) however it is available for at least half of the participants.

Figure 12: BRCA Test Topic, Analytic Categories & Sub-Categories



7.10 Scope & Study Limitations

This research is the work of a single researcher and whilst overseen by experts concurrent coding and analysis did not occur; analytic codes and categories have been developed by one researcher. Study resourcing[49] and (tiny) budget did not provide the additional researchers to conduct parallel coding. This can be viewed both as a strength and a limitation. Potential researcher bias could have be reduced by using additional researchers to during coding and analysis (Miles and Huberman, 1994). However in defence of this approach; the purpose of this work is a balance of academic pursuit and to investigate patient experience and opinion of early genetic testing.

The study has been carried out with a clinical genetics focus. However the researcher is not a genetics counsellor. Clinical understanding of genetic counselling has been acquired through observation of HBOC counselling sessions. Furthermore the researcher previously worked as a clinical research nurse within the Clinical Genetics and FHBCC teams. This approach has enabled candid discussion and an independent view of the patient experience.

The scope of this study is limited to a small number of women and a single site: participants had a diagnosis and family history of breast cancer and undertook genetic testing for high risk BRCA1/2 gene mutations, whilst under the care of NHS Tayside Clinical Genetics. It was acknowledged at the outset that sample limitations may result in some opinions, topics and themes not being captured however the

[49] The study team comprised of the Chief Investigator who supervised the study, the Principal Investigator who designed and conducted the research and analysis, and a Clinical Genetic Counsellor who assisted recruitment and provided post-interview support.

research is intended to provide a comprehensive cross-section of opinions within a short timeframe and limitations of the project. There is representation for each of the key themes for five of the six participant sub-groups / categories however saturation of key themes occurred for only one of the six sub-groups / categories.

The aim has been to capture a broad range of patient experiences and opinions. Furthermore we did not plan or attempt to standardise recruitment by matching the characteristics or number of participants by gene test result. For recruitment and analysis purposes the study population has been divided into 3 sub-groups, by gene test result:

- Identified mutation in BRCA1/2 genes
- Detected no mutation in BRCA1/2 genes
- Detected BRCA1/2 variant of uncertain significance.

Equal distribution between these categories would / could not be achieved; this reflects gene test results where the majority of tests detect no mutation in BRCA1/2 genes.

At the outset the aim was to create a more evenly distributed sample than the previous study. A major limitation in the previous study (09/S1401/25) is participant distribution. While genetic testing at the time of breast cancer diagnosis is carried out more frequently than in 2009 it remains relatively uncommon in 2015. Since the end of the previous study recruitment a small group of eligible patients had received genetic testing around the time of breast cancer diagnosis. These patients were invited to participate. In addition the Clinical Genetics team alerted the research team if / when there were any new potential participants for Category B.

An objective of this study has been to acquire data that illustrate patient experience and options associated with the timing of genetic testing:

- Category A (tested after treatment)
- Category B (tested before or during treatment).

It was anticipated that the experiences and opinions from the two Categories would differ, the primary reason for the difference will relate to urgency[50]. To reduce the impact of a potential study limitation caused by a greater number of Category A participants and to increase the scope of the study, Category A participants were asked to consider hypothetically what they would do rather than what they did in relation to genetic test at time of diagnosis. The principle reason for this commonly participants undertook the test after diagnosis and future care aims to provide tests at diagnosis to inform treatment choice. Results from the two categories may be generalised while reading the results, analysis and study conclusions although it should be borne in mind that the experiences and opinions of the study participants will differ from the experiences and opinions of future patients[51].

Saturation of Themes has been assessed pragmatically. Saturation for the 4 analysis categories has been reached for those participants who undertook testing after breast cancer treatment, with results that did not identify a BRCA1/2 mutation. However it has been assumed that Saturation has not been reached, due to the small representation, for women who undertook testing before or during treatment

[50] For example, urgency for results to inform treatment will be present in Category B and while urgency may be a feature in Category A it was anticipated that it may be a lower priority.

[51] The population for whom the research may benefit; i.e. results from this study may advise whether it is acceptable to move towards offering early genetic testing, for the high risk BRCA1/2 genes, at the time of diagnosis to inform treatment choices.

and those with results that identify a BRCA1/2 mutation or a variant of uncertain significance, regardless of test timing.

As previously described the interview schedule was adopted from a previously conducted study. While the schedule was assessed as appropriate to the current study aims, ethical approval (for this study) permitted (version controlled) amendments to the schedule. This would occur in response to new topics or themes, revealed in during data familiarisation and early analysis. However no new topics or themes were identified, therefore the schedule did not change in response to early data analysis. However later analysis did reveal a topic that had this been identified earlier the interview schedule would have been altered: the impact of the genetic test upon health behaviours. However dialogue relating to health behaviours has commonly been provided by the participants; this was not prompted by the researcher.

A significant limitation relates to the generalisability of results and while the findings are illustrative of participant experiences and opinions, a newly diagnosed hereditary breast cancer patient, for whom early genetic testing can now be proposed, should be anticipated as having a different experience[52].

It would be tempting to translate the findings into another area of genetic testing, for example:

- Predictive testing for women with high risk family history and no cancer diagnosis

[52] For example no participant received results within the 3 week guideline time for an early test.

- Hereditary cancers where genes have been identified: ovarian and bowel cancer
- Genetic conditions where acute genetic testing is available, for example Huntington's Disease.

It is advised that while similar genetic testing experiences may exist it is anticipated that opinions for the population studied will differ significantly compared to these groups, for example urgency for results may not be relevant, and for this reason the results should not be generalised. Specific research can be carried out in these fields.

In addition it is acknowledged that the population who participated may differ from the wider population of patients from a high risk family history with a personal breast cancer diagnosis. It is anticipated that the participants may be more research active, knowledgeable and willing to share their experiences, this may relate to personality or experience. No inferences can be drawn for the population who were invited and chose not to participate however it may be anticipated that the women chose not to share their experiences. Declining participation can relate to infinite factors for example personality type, social or family circumstance, however all are unknown and cannot be categorised or assumptions made.

8. RESULTS

8.1 Recruitment & Participants Enrolled

Recruitment commenced in July 2012 and concluded 11 months later in May 2013. NHS Tayside Clinical Genetics Department sent a total of 21 Invitation Letters (Appendix H) with accompanying Reply Slip (Appendix I) and Participant Information Sheet (Appendix K):

- Twelve (57%) women were recruited
- Eight (38%) responses were received within 3 weeks
- Thirteen Reminder Letters (Appendix J) with a second Participant Information Sheet were sent. Ten responses were received within a further 3 weeks.

See Table 9 for recruitment breakdown.

Table 9: Recruitment Rates

Invitations Sent	21
Responders	18 (86%)
Recruited	12 (57%)
Declined	6 (29%)
Non-Responders	3 (14%)

As described earlier (Section 7.4 Sample Design) participants have been categorised according to test timing and results. A summary of these characteristics, for the potential participant's to whom invitations were sent is shown in Table 10: Invitations Sent.

Table 10: Invitations Sent

	Test (by Category) Totals	Participants with identified mutation in BRCA1/2 genes	Participants with detected no mutation in BRCA1/2 genes	Participants with detected BRCA1/2 variant of uncertain significance
Test Result Totals (by Sub-group)	**21**	**1 / 5**	**19**	**1**
Tested after breast cancer treatment (Category A)	**15***	**1/ 3**	**14***	**0**
Tested before or during breast cancer treatment (Category B)	**6**	**0 / 2**	**5**	**1**

Code **Invitations Sent** **Anonymised data**

*** includes 2 who declined test during treatment / deferred test**

Of the 21 invitations 1 potential participant had confirmation of mutation in BRCA1/2 genes, 19 had results that detected no mutation and 1 received results that identified a BRCA1/2 variant of uncertain significance. In line with current practice the majority of invitations, 15 (71%) were sent to potential participants who undertook testing after breast cancer treatment. However, of these, 2 had been offered and declined the test during treatment (deferring the test until after treatment). The remaining 6 (29%) invitations were sent to participants who were tested before or during their cancer treatment. The previous study (09/S1401/25) provided anonymised data from 5 patients with identified BRCA1/2 mutation, 3 tested after treatment and 2 tested before or during cancer treatment (shown in blue text on Table 10).

Responses were sent using the Reply Slip (Appendix I) and postage paid return addresses envelope to the NHS Tayside Clinical Genetics Team, thereafter positive responses were provided to the research team. The research team contacted

interested potential participants using the details they supplied, most often via telephone or email. In total eighteen (86%) of the invited potential participants responded:

- Twelve (57%) were willing to give consent and subsequently participated in the study: five responded after the first letter, seven responded after a follow-up reminder letter was sent 3 weeks later.

Both response and recruitment exceeded the anticipated rates.

- Six (29%) declined participation, one of whom was willing to participate but had moved out of Tayside
- Three (14%) potential participants did not respond, despite a follow-up reminder letter being sent 3-4 weeks later. They were not re-contacted.

Study participation was discussed and where relevant an appointment arranged at a suitable time and venue to complete written Informed Consent (Appendix L) and the study interview. Enrolled participants are recorded on the Enrolment Log and Identifiable Information Log.

Where there was no response or a decline to participate was received identifiable information was not given to the research team: only participant initials and dates of letters were provided for the purpose of completing the Screening Log.

8.2 Study Data

The dataset comprises of recorded interviews, fully transcribed interviews and supporting clinical data[53] from 17 women. The interviews provide around 900 minutes of recorded data and verbatim transcriptions amount to 130,000 words. With consent 12 participants were interviewed using the topics and in-depth format that were used in the previous study (Appendix G)[54]. Interviews lasted approximately 1 hour were conducted by the PI at an agreed time and in a quiet and private location[55]. Interviews were conducted in a 10 month period and anonymised data from 5 previously conducted interviews (Ethics Reference 09/S1401/25) were obtained, with permission from the Chief Investigator. Participant distribution reflects NHS Tayside clinical practice during recruitment where genetic testing at the time of diagnosis remains relatively uncommon (See Table 8: Final Recruitment, page 115 for recruitment breakdown).

The first interview was conducted within 2 months of sending initial invitations. This was within the planned 8 weeks between first contact and interview completion however the first interview was rescheduled due to interviewer and participant holidays. The final interview was due to be conducted in April 2013 this was rescheduled to May 2013 at the participant's request. Rescheduling occurred for 5 (40%) of the 12 interviews. This could have, but did not impact on recruitment rates;

[53] Obtained from NHS Tayside Clinical records

[54] The topics and format were subject to change and could be adapted if recurrent areas which had previously not been considered become apparent during analysis, a new version controlled Interview Guide would be produced should this occur. However this did not occur.

[55] Tayside Medical Science Centre (TASC) Clinical Research Facility (CRF) or participant's home.

the original interview appointment time was instead used to produce transcriptions, carry out data familiarisation or collect clinical data.

Audio recording of each interview was conducted using an Olympus Digital Voice Recorder WS-811[56]. Only one participant chose to halt a recording, for the purpose of an off-line discussion; the participant was happy to recommence with the interview and recording. Interviews were fully transcribed to provide the full interview content, including subtleties of tone and inflections. Reflective notes of the interview & transcription experience were taken to supplement the interview / transcription data. Anonymised interviews and transcribed data from the previous study (09/S1401/25) were used to create a full transcription of each interview. Reflective notes were taken to supplement the transcription data.

Clinical data were collected from Clinical Genetic medical records within 4 weeks of enrolment:

- Year of diagnosis
- Age at diagnosis
- Treatment received
- Genetic testing: date of test and date of result
- Further treatment received up to point of interview.

Clinical data provided accuracy of dates, treatments and test results and have been used in addition to breast cancer experience data that was collected during the interview; these data supported analysis. Additionally the Chief Investigator agreed to provide clinical data from the previous study (09/S1401/25), no new clinical data

[56] Participants were free to halt the recording at any time.

was collected for the anonymised data; this was analysed in the same way as the new data.

8.3 Data Findings

Assumptions

Throughout this chapter the term patient will be used when describing an event which occurred prior to study participation. The term participant will be used to describe events or opinions that were revealed in study. Text presented in italic font are direct quotations from the participant's narrative.

The BRCA1/2 status and Test (timing) Categories apply only to this study population. While a similar distribution may be anticipated across NHS FHBCC and Clinical Genetics populations this has not been confirmed.

Quantitative Discussion

Details of age at diagnosis, the year of each participant's test, time waited for definitive BRCA1/2 gene analysis results, BRCA1/2 status, elapsed time between genetic test and study participation are shown in Table 11: Test Category, Result, Times & Treatments (see page 138).

Breast cancer diagnosis commonly occurred for the study population between age 37 and 50. Genetic testing for the study participants took place between 1997 and 2012, with 12 of the 17 patients receiving test results in less than 1 year. However when considering the total study population, the elapsed time between blood

sampling and definitive test results ranged from 2 months to 4 years, excluding one (R15) with a 10 year processing time (this commenced in 1997). Two patients (P8 & P10) waited 4 years for definitive results however both agreed to a request for a second sample after 2 years had elapsed, results for these second samples took 2 years.

A notable limitation worth mention (for clarity) is that test timing within the study population differs when compared with the newly diagnosed patient for whom early genetic testing may be proposed to inform treatment. Furthermore no participant received results that matched the current clinical guideline time of 3 weeks, for an early genetic test to inform treatment. Testing was most recently conducted in February 2012, this participant (P6) received a study invitation in July 2012 and participated in the study within 10 months of testing. It is anticipated that when testing was undertaken close to study participation that recall will be superior. It is notable that testing which took place after 2003 took less than 6 months for all but 2 patients. For one, a patient (P8) in whom repeat blood samples were requested 2 years after initial sampling; definitive results took 4 years from the first sample date in 2005. The second (since 2003) that took more than 6 months occurred in 2010, this patient (P7) waited 11 months for results.

Four participants (24%) (P3, P9, R15, R16) commenced BRCA1/2 gene testing before or during their cancer treatment. This group included the patient (R15) who waited 10 years for definitive results.

Thirteen participants (76%) undertook BRCA1/2 gene testing after primary breast cancer treatment to inform future risk for themselves and family. However two women (12%) (P5 & P12) were offered testing before / during treatment and chose to defer until after primary cancer treatment (further discussion follows). One patient (P5) who deferred testing had provided a blood sample however chose to request storage of the sample for future testing. Three of these patients (P5, P11 & P12) definitively undertook testing to inform prophylactic treatment.

Five patients received results confirming a BRCA1/2 gene mutation. One result (P3) revealed a BRCA2 variant of unknown significance. Eleven patients received results confirming no BRCA1/2 gene mutation.

BRCA Test Topic

BRCA Test data has been sub-divided into 4 inter-related thematic analysis categories containing a total of 17 sub-categories. Details of these are shown in Figure 12: BRCA Test Topic, Analytic Categories & Sub-Categories (see page 124 - reference to this figure will assist the reader's progress through these study findings).

A comprehensive representation that exposes the breadth of opinions conveyed in relation to the study aims and objectives follows. Thematic analysis categories and sub-categories have been used throughout to assist analysis and where possible these are used for data presentation purposes. Each category section starts with key findings and themes, thereafter more detailed discussion, using sub-categories, follows.

Table 11: Test Category, Result, Times & Treatments

Participant / Age @ Diagnosis	Test Category Before / During or After BC Treatment	BRCA1/2 Status	Test Year	Time for Results (from first blood sample)	Time from Test to Study	Primary Treatment	Risk Reducing & Subsequent Surgical Intervention
P1 / 37	After	No BRCA	2011	4 months	11 mths	Mastectomy Chemotherapy	
P2 / 48	After	No BRCA	2010	5 months	2 years 4 mths	Lumpectomy Chemo & Radiotherapy	Mastectomy Reconstruction
P3 / 45∞	Before	BRCA Variant of Unknown Significance	2011	2 months	9 mths	Chemotherapy Lumpectomy	
P4 / 37	After	No BRCA	2009	2 months	3 years 2 mths	Lumpectomy Chemo & Radiotherapy	Bilateral Mastectomy Reconstruction
P5 / 42	After (deferred)	No BRCA	2009 ('07*)	4 months+	5 years 1 month	Chemotherapy Mastectomy & Reconstruction	
P6 / 47	After	No BRCA	2012	2 months	9 mths	Lumpectomy	
P7 / 45	After	No BRCA	2010	11 months	2 years 8 mths	Mastectomy	
P8 / 61&64	After	No BRCA	2005 & '07	4 years+	5 years 4 mths	Lumpectomy	Mastectomy Reconstruction
P9 / 43	Before	No BRCA	2010	6 months	2 years 10 mths	Bilateral Mastectomy Reconstruction Radiotherapy	(Mastectomy)
P10 / 42	After	No BRCA	2001 & 2003	4 years	11 years 1 month	Chemotherapy Mastectomy Radiotherapy	Reconstruction
P11 / 45	After to inform	No BRCA	2010	3 months	2 years 9 mths	Chemotherapy Lumpectomy	
P12 / 50∞	After (deferred)	No BRCA	2011	5 months	1 year 10 mths	Chemotherapy Lumpectomy Radiotherapy	
R2 / 32	After	BRCA	2003	2 years 11months	6 years	Bilateral Mastectomy Chemo and Radiotherapy	(Mastectomy)
R11 / 43	After	BRCA	1998	2 years 7 months	11 years	Chemotherapy Mastectomy Radiotherapy	Prophylactic Mastectomy
R14 / 46	After	BRCA	2002	6 months	8 years	Bilateral Mastectomy	(Mastectomy)
R15 / 48	Before	BRCA	1997	10 years	13 years	Chemotherapy Bilateral Mastectomy	(Mastectomy)
R16 / 38	Before	BRCA	2008	3 months	2 years	Chemotherapy Mastectomy Radiotherapy	Prophylactic Mastectomy

Table Key: * Blood sample provided, patient deferred testing until after treatment
+ Repeat sample provided 2 years after initial sample
∞ Triple negative

8.4 Genetic Testing

Key Findings: Why Women Undertake Genetic Testing

In this study population, the proposal for BRCA1/2 genetic testing is ordinarily made by a healthcare professional, although less commonly the patient requested the test. Participants consistently undertake the test with the aim of informing primary cancer treatment or risk-reduction interventions.

Recurring throughout the Genetic Testing dialogue are the themes of maximising survival, fear, protection and responsibility. These closely inter-related themes impact participant choice throughout genetic testing and treatment decisions.

The dominant reason for women in this study undertaking the test is to inform treatment decisions. Maximising survival is presented as the recurring theme that impacts the decision. A test undertaken close to diagnosis is consistently taken to inform primary treatment and subsequent prophylactic therapies. However tests carried out after primary treatment are typically initiated, by women in this study, to obtain genetic information to guide cancer risk-reduction decisions.

Within this study population the coping style that is adopted by the patient, when the test is proposed, influences whether patients actively seeks genetic information or accepts a proposal for testing. While it is understood from participant dialogue that coping style is not fixed, those who assume an information seeking style, at diagnosis or when testing is considered, commonly request the test. Conversely women who, at this time, adopt an avoiding coping style readily accept the proposal for testing and are less likely to seek out the test.

An important factor that influences the uptake of BRCA1/2 testing, particularly when undertaken after primary cancer treatment, is the provision of genetic information to inform and offer protection for at risk family members. While not consistently related to treatment choices responsibility and family protection are important themes. However participants identify that early BRCA1/2 status information to inform treatment will be higher priority and importance than genetic information for the family.

Specific themes that relate to the test and informing treatment are '*just take it*', '*prepare for bigger surgery*', getting '*the right treatment early*' and '*quick preventative treatment*'. Timing of the test is considered less important when considering cancer risk-reduction, prophylactic interventions.

Preparing for Results

Participants describe anticipating extensive surgery, until genetic results are available to inform personalised treatment. Overwhelming, within the study population, preference is afforded to minimising the number of surgeries and where possible carrying out risk-reducing prophylactic interventions at the same time as primary cancer treatment. Where prophylactic therapy is indicated, in the presence of a BRCA1/2 mutation, participants choose to undertake treatments quickly, with the aim of avoiding cancer recurrence.

Protection, for self and family, is a theme that relates to disclosing the decision to undertake testing, before results are available. Participants indicate that the main factor that influences withholding this decision is protecting family, from worry about

results. An alternative proposal is that fear guides this choice; external opinions may alter their test decision and previously supportive relationships can be impacted by the test and genetic uncertainty. Furthermore participants identify that healthcare support, for the patient and family, can assist decision making throughout the testing process.

Impact of Genetic Results on Treatment Decisions

Women who undertake early genetic testing to inform treatment and prophylactic decisions, welcome test results, even when a BRCA1/2 mutation is identified:

> *R15 I was grateful that I knew and it confirmed what I needed doing.*

For these women genetic results that identify a mutation are commonly received with '*no surprise*':

> *R16 it came back positive almost straight away … I had the mastectomy and partial reconstruction ... I've had my belts and braces radiotherapy … surgery, within the next three months (prophylactic mastectomy with reconstruction) … I've had the chemo.*

The results facilitate a clear decision and personalised treatment pathway.

Conversely where no mutation is identified or a variant of uncertain significance is identified participants describe a range of responses. However a false sense of security the dominant theme:

> *P7 there wasn't anything … maybe that's a sort of false security.*

Correspondingly they describe uncertainty:

> *P5 would have been better knowing, one way or the other … if they could have identified something.*

The results report no mutation. However commonly this result is not considered to be definitive, participants worry about a false negative result:

P9 it's come back as nothing … I do think they have just not found it yet.

Participants consistently describe disbelief, they describe having a genetic mutation that has not yet been identified, when their result identifies no mutation or a genetic variant of uncertain significance.

In response to a test that detects no mutation or a variant of uncertain significance participants and surgeons can choose breast sparing procedures. However the dominant themes a false sense of security, worry about a false negative result and maximising survival are fundamental factors in determining treatment decisions for these women:

R3 even though it was negative I still wanted to go ahead with it (double mastectomy) … it was a relief knowing that, I don't really know if it was a relief because I know it made it less likely …there could still be something … it wasn't conclusive.

Within the study population psychosocial factors, including family cancer experience and fear of recurrence, motivate patients to undertake larger surgery that when based on established genetic risk this decision may be unwarranted. For these women treatment decision conflict can be a response to a test that identifies no mutation or a mutation of uncertain significance.

Coping style adopted at the time of treatment planning, is identified as a significant factor that influences treatment decisions. Participants who display an information seeking style are more accepting of the surgeon's treatment proposal. Conversely those with an avoiding coping style assume a more active role; for these women, psychosocial factors appear to play a greater role in treatment decisions.

Overwhelmingly participants support early genetic testing to inform treatment:

R16 giving information is much more proactive… it's a no brainer, that's what you have to do.

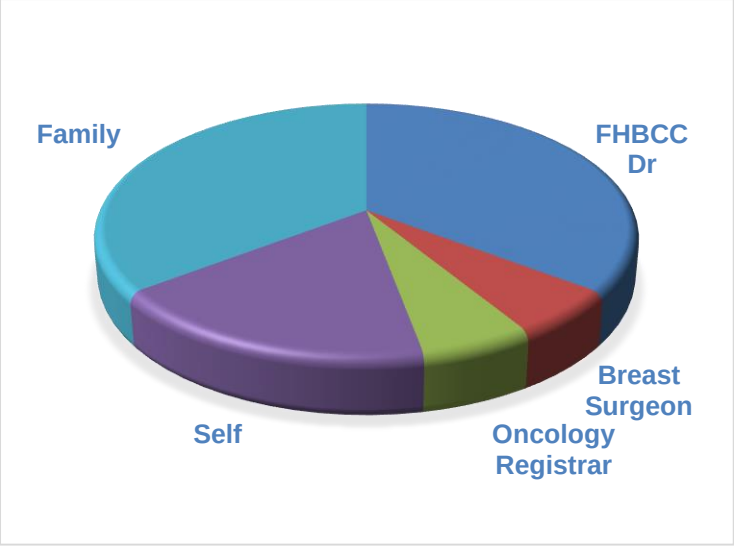
Furthermore they demonstrate acceptance of the purpose and function of early testing.

A presentation of the Genetic Testing sub-categories and evolving themes follows.

First mention of the BRCA test

Throughout the narrative participant's describe who first mentioned genetic testing or their initial thoughts about gene testing. Responses are organised into 3 groups: family, health care professional and self. The relationship between these groups is displayed in Figure 13.

Figure 13: Gene Testing & the First Mention or Thoughts



Health Care Professional

Predominantly BRCA1/2 gene testing is proposed by a health care professional, this commonly precedes the patient's consideration of genetic testing:

> *P9 we've been discussing your case and we were looking at it all and we would like you to speak to genetics.* (Breast Surgeon)

Acceptance of genetic test proposals within the study population are high:

> *R14 You sort of depend on the doctors leading you in the right direction hoping that they know what is the best course that you are going to take … if they say genetic testing, you would probably agree to get it done.*

Doctors and healthcare professionals are regarded for their role in promoting the best for the individual[57]. Most commonly, individuals who do not actively seek information, those with an avoiding coping style, indicate a ready acceptance of a test proposal.

Contrastingly participants describe surprise and depict taking action to include the genetic test discussion in treatment consultations:

> *P9 if no-one had spoken to me about it … I would have brought it into a discussion at some point.*

At the time of diagnosis this participant predominantly displays an avoiding coping style although she describes action, more related to an information seeking style that would be adopted had she required[58].

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[57] Notably one doctor, a consultant breast surgeon and FHBCC consultant, is consistently described as recommending genetic testing. Furthermore supporting data revealed that this doctor has regularly cared for members of the study population. However it could not be established whether she was involved in the genetic test proposal for each of her patients.

[58] However for this participant a breast surgeon proposed genetic testing in response to age of diagnosis and tumour characteristics; she was not compelled to request testing.

Self

Less often participant's describe that they had the first thought or were first to raise the topic of genetic testing to inform treatment decisions. An information seeking response is displayed:

> *P3 When I got my confirmed diagnosis … at that point I spoke about genetics… I've always thought about genetics … it was discussed straight away … within 2 days of my initial diagnosis … after a bit of research I realised that if it was genetic I would be more, it would be more suitable to have a double mastectomy.*

Participants who propose genetic testing typically display an increased awareness or knowledge of personalised medicine techniques:

> *R15 I read about it, always taken interest in research because of family (history).*

An information seeking coping style is associated with these actions; seeking information to address the cancer risk.

Family

More exceptionally a family member may suggest that their relative, the patient requests genetic testing:

> *P1 it was really my cousin on my dad's side … they wanted to know, it had to start with me, I'm the one that's had the cancer… it was her ' is it ok if you go & see a geneticist?' 'Aye, fine, no bother.'*

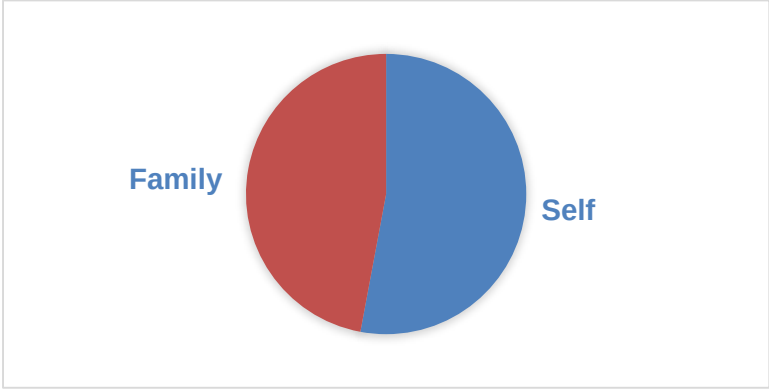
However it is anticipated that this request would have a lower priority for the patient had testing been carried out before primary cancer treatment.

Reasons for BRCA test

Similar to first mention of testing, the reasons presented for undertaking the BRCA1/2 genetic test fall into 2 groups displayed in Figure 14. However cross-over

occurs and multiple rationale are commonly presented in participant dialogue. The participants identifying self, predominantly identify treatment decisions within their dialogue.

Figure 14: Primary Reason for the BRCA Test[59]



Self

The dominant reason for participants proceeding with the BRCA1/2 test relates to the individual. Maximising survival is the dominant theme:

> *R2 I needed to know to protect my own self, for my future health … my first priority.*

Within dialogue relating to self-protection, participants emphasise the importance of survival, commonly this dialogue conveys strong emotion. An information seeking coping style is attributed to patients who seek genetic information. Information helps these women to cope with their diagnosis.

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[59] An unanticipated response (unrelated to treatment decisions) that was provided in addition to self or family reasons for the BRCA1/2 test, related to societal and scientific benefit. Women reported that these extra factors were part of the motivation to undertake genetic testing:

> *P2 anything that I can do to help other people.*
> *R14 Mostly for the doctors … or research … rather than my benefit … to see scientifically.*

A factor that may have contributed to this response is that NHS Tayside clinical facilities are research active and patients are regularly exposed to research trials. Additionally the field of breast cancer is highly research driven. Progress within the field of Clinical Genetics relies on knowledge, new techniques and technologies. Genetic material can be used within research will increase scientific knowledge.

The survival theme is a widespread motivation for undertaking the test; it extends to cancer risk-reduction and risk-reduction interventions to improve prognosis:

> *P5 I agreed to have the actual test done to try and help me make up my mind whether I should go through it all again to the other side (mastectomy).*

The importance of appropriate cancer risk-reduction, including prophylactic therapy, surveillance and health behaviours, in the presence of a BRCA1/2 mutation is well established. Conversely the confirmation that a mutation is not identified can provide reassurance that breast conserving surgery is appropriate. Furthermore, continuing, or adopting, surveillance and health behaviours to reduce non-BRCA HBOC risk is appropriate for women where no mutation is identified.

The focus on self is at times described as a selfish act:

> *P3 the reason for me getting the genetic testing was 99% to do with what my treatment would be, nothing else …if they didn't do the right treatment for myself I might not be here so that is not selfish because they (family) need me.*

However self-protection is later justified as survival with additional family protection benefit.

Family

Unsurprisingly, throughout the study, family is a recurring theme and is universally cited as a significant factor in undertaking the BRCA1/2 test; consistently participants provide family reasons within their narrative. This is understood to relate to the self-protection theme, from the perspective of getting the best treatment:

> *P11 my children were so young, they were 4 and 2, my priority was staying alive as long as I possibly could.*

Self-protection is further emphasised by participants who indicate having dependent children.

Additionally BRCA1/2 status information for family-protection is a common response:

> *R14 knowing what gene they had and what steps to take and what course of treatment would be more appropriate.*

However it is acknowledged that experiences and opinions of the study population may differ from an early genetic test patient group:

> *R11 we can treat you different if we know it's genetic … and if you've got any sisters or cousins you could pass on that information to them, then they have a choice.*

Participants who undertake testing after treatment identify that BRCA1/2 status information for the family will be lower priority, than early genetic information to inform their treatment.

Inform treatment?

Primary cancer

Within this study population genetic testing to inform primary cancer treatment is less common. Results pertaining to primary cancer treatment are presented for participants who undertook testing before or during treatment. For two participants results were available to inform primary cancer treatment. Data relating to hypothetical primary cancer treatment questions are presented later in the chapter (Section 8.6 Early Genetic Testing). Clarification of treatment undertaken is displayed on Table 11: Test Category, Result, Times & Treatments (see page 138).

Participants acknowledge that early genetic testing preformed in response to a treatment planning discussion provides information that can assist appropriate and personalised treatment:

> *P3 it will influence consultants decisions, it's not just your decision, they would have changed their mind … 'if you do get genetic tested and it comes back positive BRCA1 BRCA2 we would change our mind' (Surgeon / Oncologist / Radiologist).*

Reassuringly the narrative displays a relationship where the patient and surgeon decide the most appropriate treatment plan. Similarly when proposing genetic testing:

> *P9 'we want you to speak to the genetics' (Surgeon)… I think they wanted me to speak to genetics to talk me into having both my breasts off.*

Recurring throughout the data the health care professional is viewed as an advocate, promoting tailored treatment that offers maximum patient benefit and when this is based upon established genetic risk:

> *P3 I don't really think you have a choice. I think the choice is made for you unless you put up some reasons for it to change … they are qualified they have the (pause) expertise, I don't.*

Coping style is identified as a significant factor when treatment decisions are made. Women who adopt an information seeking coping style, generally accept the surgeon's treatment decision proposal. Conversely women who adapt an avoiding style during treatment decision-making commonly propose, or adopt an active role in deciding, the surgical intervention.

Consistently early genetic test results are welcomed:

> *P3 it just made such a difference to me … even if it had come back positive gene it still would have made the massive difference … whole treatment would have been changed.*

A variant of uncertain significance result follows a similar treatment plan to a no mutation result. Dialogue displays that the result established clarity for treatment and

in response the BRCA1/2 result breast conserving treatment can be safely undertaken:

> *P3 The decision, their thoughts were always to do a lumpectomy and in my eyes I would go along exactly with what they think … the only change it would have been is if it had come back positive. So there was no real discussion afterwards because to me it was black or white. If it came back positive … I'm going down one route and if it came back negative I would go down the other route … so the decision was made a long time before.*

The dialogue presents the surgeon's chosen treatment plan, identified prior to testing, being implemented following the receipt of the BRCA1/2 result. An information seeking coping style is adopted by the patient at the time of treatment decision-making; the genetic result confirms for the surgeon and patient that the plan is appropriate.

Contrastingly when a test identifies a BRCA1/2 mutation breast conserving surgery will not be proposed.

> *R16 I had the mastectomy and partial reconstruction*

The result provided genetic cancer-risk clarity and a definitive, more extensive surgical treatment, including prophylactic treatment will typically be recommended. Furthermore, reconstruction incorporated with primary treatment is increasingly considered by surgeons and patients. :

Within this study population results are not consistently available to inform primary cancer treatment. Rarely testing commenced prior to the use of modern genetic techniques and while aware that the result would not be available to inform treatment this patient chose to pursue testing and wait for results:

R15 in my case it didn't because it was such a long delay … that was something that I'd decided anyway (bilateral mastectomy) it didn't bother me at the time, I knew it was the right decision

While this 10 year wait for results is an extreme example, it emphasises the impact when results (that are required and anticipated) are not available to inform treatment. Support for genetic testing to inform / confirm treatment is however evident:

R15 I was grateful that I knew and it confirmed what I needed doing even though I was doing it anyway … .the knowledge would help you to decide whether to have a mastectomy or not.

Irrespective of the prolonged wait for results the value of early genetic information to inform treatment is defended by the participant. This benefit was not afforded to this participant but can be anticipated for future HBOC patients.

A more exceptional experience indicates that genetic testing is not be required to inform primary treatment:

P9 I said 'well can I have both breasts removed' … 'absolutely and in that case you can have a, we can do an instant reconstruction' (surgeon) … I didn't go back to see (genetics) till later… I think we just … could … have cut out the middle man if you will excuse me referring to genetics like that... no urgency 'you've got enough to be dealing with, we'll deal with this later on' (surgeon)

The culture for early genetic testing was however new:

P9 I was advised against doing it, against waiting, delaying … they were saying there is time, 3 weeks waiting for a genetics test to come back … I was booked in …these huge hours in theatre were booked in well in advance.

While this experience is not one of the oldest it is not considered to be in-line with current practice. Results would have been available before surgery (4 weeks after diagnosis) and surgical scheduling whilst complex is today more adaptable. Notable throughout this participant's narrative is her rationale for extensive treatment:

P9 it's breast tissue … it is a bit of my body that you can cut off and chuck in a bin, I would rather it cut off and chucked in a bin than the chance of it recurring … my sister's experience definitely, and other people … we know who have had breast cancer and have had lumpectomies or single mastectomies and had the recurrence … I personally don't understand why anybody ever keeps their breasts if you've got it and they can cut them off, take them off (expressive) … people keep dying …that was completely my main reason… because of my family history I was very clear I wanted everything removed

The strength of this dialogue may conceal a false sense of security and disbelief in response to the genetic test that identified no mutation. Correspondingly maximising survival and psychosocial responses to the result are identified as factors motivating treatment choice. Alternative lesser surgeries were proposed:

P9 a lumpectomy…I don't want that … or a single mastectomy I didn't want either … there is no (way), I would be lop-sided.

It is not established, the participant does not indicate, whether an early test result that identified no mutation would have altered treatment choice:

P9 I love the way all of mine worked and the way it has all gone and it is fabulous … I kinda do think at some point you will find something else.

This treatment plan (double mastectomy and immediate reconstruction) was made and carried out before receiving the BRCA1/2 test result. The extensive surgery undertaken offers a significant risk-reduction and acceptable cosmetic result although based on the established genetic risk it is thought to be unwarranted.

Risk-reducing treatments

Genetic testing within the study population is predominantly undertaken to inform cancer risk and identify subsequent risk-reducing interventions. However when considering early testing and the potential impact of a BRCA1/2 mutation, identified close to diagnosis:

P1 I would like to have known at that time … make an informed decision, you could have the double mastectomy.

The anticipation of undertaking extensive primary surgery that incorporates prophylactic interventions is a recurrent theme. Consistently participants support the option for genetic information at the time of primary surgical treatment:

P3 It would have been very hard having a lumpectomy and then being told that it was genetic … positive BRCA gene because then to make the decision to go back again and have more surgery is a big decision

Genetic information facilitates appropriate treatment decision-making; this dialogue emphasises the recurring theme: Participants overwhelmingly value the option for personalised treatment, undertaken early to reduce cancer risk and minimise the need for further interventions.

Less commonly participants chose to store their sample and defer testing until after primary treatment. Postponed testing occurred where primary treatment would be appropriate if a BRCA1/2 mutation was present:

P5 I didn't want that at the time, I thought 'I'm doing the surgery anyway (mastectomy), I don't need to know'.

Genetic information to determine subsequent risk-reducing interventions is a common theme. Regardless of timing, the test provides personal genetic and cancer risk information to assist risk-reduction decision making. Significantly this participant, in response to a no mutation result, did not undertake additional risk-reducing surgical interventions.

Recollection of a consultation identifies the predominant response when no BRCA1/2 mutation is identified, after primary cancer treatment:

P1 'Well you're fine' (surgeon in response to result) … I was asking 'should I have this breast off?' … 'No you don't need to, it's a massive surgery' (surgeon's response) 'you've got to think of … your body'. 'You don't need to tell me!' (very expressive) I've been through it already (mastectomy). So at the moment I'm keeping things at the moment.

Emphasis placed on the impact of surgery and confirms that further risk-reducing surgery, commonly a prophylactic mastectomy, is clinically unwarranted when a results identifies no mutation or a genetic variant of uncertain significance. Clinical guidance may indicate breast conserving treatment, ongoing breast surveillance screening and positive health behaviours. Prophylactic breast intervention will not usually be proposed. However when breast conserving treatment is undertaken a false sense of security and treatment-decision conflict can ensue:

P11 I would have felt more comfortable had they just removed the whole breast and I still have that kind of feeling … I was like 'oh, mmm was that safe' … I still have this fear of not having the whole lot taken away … I would have been happier I know that sounds really bizarre nobody wants to have their breast removed but I would rather remove the offending item and get rid of it (cancer risk) completely.

Despite disbelief and conflict this participant undertook no further risk reducing surgical interventions, the BRCA1/2 result informed treatment.

Correspondingly for participants with no mutation, who subsequently choose to undertake prophylactic bilateral mastectomy, a false sense of security is considered to be a significant factor in the decision:

P4 even though these results were negative It was still something that I quite strongly wanted … I still wanted to go ahead with it.

The dominant themes, maximising survival and disbelief, are identified as fundamental in the decision to undertake prophylactic treatment when no mutation is

identified. Associated factors include family history cancer experience and family protection.

Conversely where testing identifies increased risk patients consistently undertake prophylactic therapies. In response to an identified BRCA1/2 mutation, regardless of timing of the test, these women undertake prophylactic treatment as soon is feasible. Furthermore where clinically appropriate, this can be undertaken at the same time as primary cancer treatment, for example a bilateral mastectomy:

> *R2 I was keen, have the 2nd breast removed at the same time. I just didn't want to have to cope with it twice ... they were talking about radiotherapy & chemotherapy, the thought of going through an operation, going through all that treatment, getting out of that and then developing another breast lump and having to start again. I wanted to get on with my life, it was me pushing for that.*

However in response to a BRCA1/2 mutation identified before primary cancer treatment it may be appropriate that additional prophylactic interventions are undertaken after primary cancer treatment:

> *R16 I'm programmed in for to have surgery, within the next three months for that (mastectomy with reconstruction).*

Cancer therapy considerations can impact treatment pathways; for example radiotherapy has a negative impact on certain types of breast reconstruction.

Participants identify that the impact of cancer recurrence and additional treatment is considerable. Women propose risk-reduction (for cancer recurrence) to minimise subsequent health and psychosocial effects that result from cancer diagnosis and treatment: maximising survival. A similar (but lesser) effect can be anticipated in response to prophylactic and reconstructive surgery, i.e. combine surgeries.

In the presence of HBOC women may have undertaken oophorectomy prior to their breast cancer diagnosis, based on family history and predicted genetic risk:

> *P6 doctor … suggested getting your ovaries removed … (I) got that done.*

Similarly they consider prophylactic ovarian surgery before genetic testing:

> *P2 I'd been talking about the ovarian cancer … (surgeon) suggested getting in touch with the counsellor to talk about it.*

Genetic results can inform the decision:

> *P9 it's good not to have the gene … the chances of ovarian cancer would be heavy (if BRCA1/2 identified) so it took away the option of having to think do I go through another operation … which I would have done (oophorectomy), beyond any doubt.*

The dialogue indicates intention to undertake prophylactic ovarian surgery. However when results identify no mutation, ovarian surgery is not undertaken, demonstrating that the test results are used to inform treatment.

In response to an identified BRCA1/2 mutation additional prophylactic ovarian surgery is considered:

> *R16 I think I've got a wee bit longer to think about that … I don't think that's immediate … by about the time that I'm about 43 I've really got to think about that, before the menopause because my grandmother had ovarian (cancer).*

However oophorectomy is generally undertaken soon after a mutation is identified:

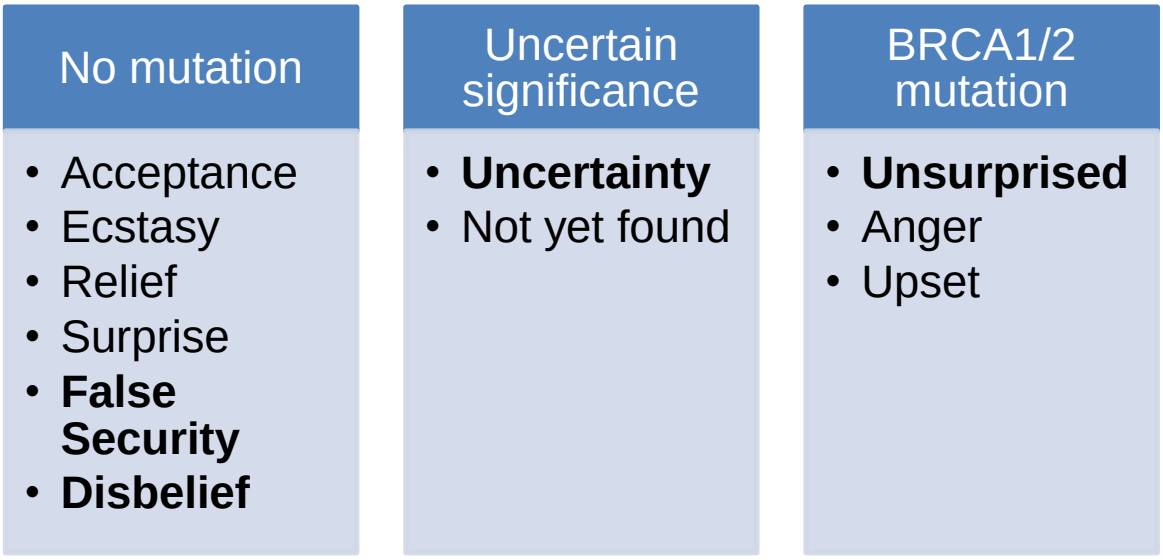
> *R14 I then had to decide whether to have my ovaries taken out because of the genetic strain, so I decided to do that as well + get my ovaries taken out About 3 months (after genetic test result)*

Women who had undertaken oophorectomy prior to genetic testing, based on family history and predicted genetic risk, are reassured that undertaking the procedure was appropriate when a mutation is identified.

Reaction to BRCA test result

Response to results and treatment responses correspond to 3 general groups which relate to the test result. Within each group a range of reactions were reported, some are short-lived responses while others endure and impact treatment choices. Figure 15 details the responses with dominant responses shown in bold.

Figure 15: Response to Results



No mutation detected

Responses to this result ranged from acceptance to ecstasy and relief to surprise. The dominant theme within the group of participants who received a result that detected no mutation is a false sense of security. Consistently women report that their mutation had not yet been identified and that the genetic mutation may be identified in the future as techniques improve. Uncertainty, disbelief and worry about a false negative result are understood to impact the treatment choice for this group of participants.

Additionally participants provide familial experience accounts of cancer recurrence, these are thought to be closely associated with this false sense of security. This description is typical, displaying first relief then disbelief and worry about a false negative result:

> *P2 It was a relief, in a way to know that they hadn't found anything but you still have this doubt, everything is changing so quickly, you still wonder, maybe there is something, it is so strange that 4 of us have had that type of cancer (laugh), alarm bells start ringing.*

Patients receive counselling before the test and after receiving a result of no mutation detected to advise that current testing only identifies a BRCA1/2 mutation in around 20-25% of families with a strong history of breast or ovarian cancer (NHS Tayside Clinical Genetics). Furthermore genetic blood samples are retained for future testing.

A false sense of security and worry about a false negative results is therefore not unwarranted as patients with this result may have an unidentified inherited susceptibility. An increase breast cancer risk is acknowledged and increased screening is provided for the individual and family members. However participants frequently describe disbelief and consider the result as inconclusive, leaving them with uncertainty:

> *P5 in hindsight maybe it would have been better knowing, one way or the other*

Fear of recurrence in response to treatment choice is reported:

> P11 *I still have this fear of not having the whole lot taken away*

Uncommonly anger is described in relation to the potential uncertainty of a result that detects no mutation:

> *P9 it annoyed me, 'oh for goodness sake get it right ' you know 'you either have or you don't' (laughing) … I thought 'oh god, you're putting people through that & then you are still saying after that you still don't know.*

The variety of emotional responses associated with a result that identifies no mutation (see Figure 15: Response to Results, pg 157) are associated with uncertainty and fear. Frequently the response is amplified by factors such as age, prior cancer experience, support, knowledge and coping style. Each of these factors can impact treatment decisions.

Variant of uncertain significance

A range of emotional responses are presented in response to results of uncertain significance:

> *P3 I don't really know if it was a relief because I know it made it less likely… but I know there could still be something. The fact that it wasn't conclusive is making me like 'ohh'!*

A false sense of security is dominant. Patients with an uncertain significance result are informed by NHS Tayside Clinical Genetics to anticipate future developments and re-testing. Such information may further confound a false sense of security. Treatment decisions in the presence of a mutation of uncertain significance are personalised and based on established tumour characteristics.

Women with a genetic variant of uncertain significance may have a variant that is considered normal, one that is associated with an increased breast cancer risk or more simply a variant that is not known. FHBCC screening and risk reduction health behaviour information will be offered however the response to uncertainty may be similar to a false sense of security. Some will view the result in the same way as a BRCA1/2 mutation, with the associated increased risk. However medical response to this result may not support an identified mutation treatment plan.

BRCA1/2 mutation identified

Overwhelmingly the reaction to an identified mutation in BRCA1/2 genes is 'no surprise'. The following dialogue captures a common response:

> *R11 being told that (BRCA mutation) wasn't any great revelation.*

Anger is a widespread response to a BRCA mutation, albeit for a short time:

> *R16 I did feel, five minutes angry. You can't let it … I focused on getting the cancer sorted.*

The psychological process of coming to terms with the presence of a highly penetrant gene is at times emotionally charged. A number of significant factors, including age, family cancer experience, knowledge, and coping style impact the process. However when faced with a cancer diagnosis around the time of receiving a genetic result, participants consistently focus on the cancer treatment and recovery, and not the genetic result:

> *R16 you had to be so focused on getting the cancer treated, sorted. I focused on getting the cancer sorted…You know you accept things happen… there's no point in me sitting there thinking 'why the hell?' That wouldn't have got me better so I focused on that… I was grateful that I knew* (BRCA1/2 status) *and it confirmed what I needed doing even though I was doing it anyway* (neo-adjuvant chemotherapy, mastectomy and subsequent prophylactic mastectomy).

Within the dialogue, the participant identifies that confirmation of BRCA1/2 status provides reassurance, and that the treatment pathway can be personalised to maximise survival and prognosis. This testing pathway (test before treatment) uses the model anticipated for newly diagnosed HBOC patients. Maximum patient benefit, within future clinical care pathways, is anticipated when early BRCA1/2 testing informs treatment.

Family experience and (when known) a relative's BRCA status will affect the patients expectations. If for example a first line relative has previously received a negative result and the patient receives a positive result their response may be unpredicted:

> *R16 (for) a very, very short period … a wee bit angry that the letter we got 4 years previously from my mum hadn't suggested that the test was a moving ...angry that I hadn't had the chance to have the test, if I had known test was getting better, I would have asked. Anyone with similar circumstances who got a letter (previous negative result) … traced and contacted and told test much better than it was before … get them before they get cancer … if any other families could be caught, traced and told test getting better.*

A realistic expectation of the time that will be required for genetic analysis and the accuracy of current testing is now provided, in counselling and in writing, before and after the test (NHS Tayside Clinical Genetics).

Support During & After Testing

Support is considered to be important for the participant and / or family during the genetic testing process. Family support is commonly viewed as relevant and important during the genetic testing process:

> *R2 people react in different ways …it depends on the support you've got around you with family.*

It is not clear, within the study dialogue, however it is predicted that family support extends to assisting patient's treatment choice.

Support is consistently expressed in respect of health care professional provision for either the patient or the family during the testing process. This type of support relates to the often complex genetic information that is provided before, during and after the test:

R11 speak to Macmillan nurse and go through everything again (genetic results).

Support to assist treatment choice is a fundamental role of the Breast Care Team.

However less frequently it is acknowledged that despite an open-door policy patients choose not to contact Clinical Genetics:

P11 In the letter it says 'always call me'… I don't want to be a pest I would have liked to speak to genetics again.

Within future clinical pathways the role the wider Breast Care Team in assisting treatment decisions will require robust policy to ensure that patients have the necessary support to make treatment decisions. In response to a result that identifies no mutation or a mutation of uncertain significance additional follow-up genetic counselling support may be needed to explore responses, for example a false sense of security and disbelief, that participants reveal.

Impact for family

The decision to involve family members early in the testing process is not always easy. Predominantly women in this study chose not to involve family members in the test decision. Where early testing is undertaken to inform treatment comparable choice is anticipated.

Not informing the extended family provides protection to the patient; their decision is not questioned or altered by external (relative's) opinion. In this example a clear decision is reached at the time of testing however in later reflection the decision and familial impact are questioned:

P9 I never sat down & gave anybody any options. Oh god, that's maybe really selfish?

Self-protection is afforded when family opinions are not invited. Fear that relative's attitudes and opinions may alter the genetic test, and subsequent treatment, decision is an underlying assumption. The dialogue demonstrates that the BRCA1/2 test is taken to inform treatment decision and not to provide genetic information for the family.

Additionally the decision not to inform safeguards the family; they have no knowledge of the wait for results or potential impact for their health. Responsibility and protection are common features that motivate withholding information about the genetic test:

> P2 *it's like saying you've got cancer, carrying the cancer gene, so I don't want to say that to them, alarming them*

The dialogue displays a widespread participant opinion: the process of undertaking the genetic test displays an increased risk for developing breast cancer. Women do not wish to unduly worry relatives of a potential risk but would rather wait until the result is available to give a more definitive risk. Responsibility for the family is a recurring theme relating the uptake of BRCA1/2 testing however it is not considered to impact treatment choices, except in relation to survival. Familial relationships and roles adopted by the patient are considered fundamental factors that influence the decision to communicate information about an intention to undertake a genetic test.

Less commonly the impact for the family starts when the genetic test is first considered and the family are involved in the BRCA test decision:

> *P3 we are very close … it was discussed (BRCA testing) straight away … within 2 days of my initial diagnosis.*

In response to this information relatives express concern regarding the potential impact of BRCA test (for them):

> *P3 she (sister) immediately said that she would want tested.*

While disclosure occurred within a close relationship the patient risked exposure to additional psychosocial stress furthermore this previously supportive relationships may become strained.

Throughout the dialogue little is found in relation to family members and treatment choice, except where a parent or sibling has a previous cancer diagnosis:

> *P11 my sister had a mastectomy and my mum had a mastectomy... I was very much up for having the double mastectomy if it came back positive.*

In such situations a similar treatment choice, that undertaken by relatives, may be considered and is anticipated by the patient.

Consistently familial consequences of genetic information are viewed in relation to significant life and health impacts and not the (patient's) treatment decision. However the greatest impact is realised when a BRCA1/2 mutation is identified though infrequently this is in relation to the patient's treatment. However the process of informing family members can be difficult:

> *R15 I've got two daughters and a son. It took me a few weeks to tell them … I was quite upset when I was telling them (BRCA result).*

Disclosing genetic information may gain greater familial understanding and appreciation of their hereditary cancer:

> *R2 from my mum's point of view… it has brought up a lot for her and we've learnt a lot about what she had to cope with … things fall into place for her as well now.*

Revisiting a relative's cancer journey and treatment pathway however may impact treatment choices.

Siblings are infrequently mentioned in relation to treatment decisions. However they are commonly the motivation for seeking BRCA1/2 status information and the presence of a confirmatory result amplifies the importance of testing a sibling:

R16 my sister … we felt it was imperative that we get her checked.

While the motivation for predictive testing is sound the psychosocial implications of predictive testing may not be fully considered by all concerned:

R2 I know that from my sisters point of view, her getting tested for a gene put implications on her if she was wanting to re-mortgage her house and life insurances and things like that and if she had been diagnosed (identified BRCA gene mutation) with it that would affect her getting all these … I hadn't really thought but from my position, because you definitely have the cancer, your priorities do change and you have to do the survival bit first and then deal with all the other things later.

Additionally participants identify children in relation to treatment choice:

P11 my daughter was 2 and I have a niece so for their sakes … my priority was staying alive.

Maximising survival is the dominant theme when considering family and impact of the test on treatment decisions.

8.5 Test & Results

Throughout this section results relate to the patient experience. Subsequent data that relates to hypothetical questions is presented later in this chapter (Section 8.7 Early Genetic Testing).

Key Findings: The Impact of the Test & Results

Waiting for Results

The blood sampling process is overwhelmingly viewed, by participants, as acceptable. Commonly the women make light of the process, although less typically a strong emotional reaction is reported. This is understood to relate to establishing cancer risk and responsibility for self and family. The importance of early sampling is recognised by participants; ensuring that cancer therapies do not compromise DNA quality.

Reinforcement of reasons for undertaking the test recur throughout dialogue, that relates to waiting for results. The '*what will they do?*' theme indicates that patients recognise that genetic information increases bespoke treatment options, both when considering primary treatment and risk-reducing interventions. Additionally, and in support of the decision to undertake BRCA1/2 testing, while '*you don't want to hear it*' participants propose that early testing is '*a no brainer*' that is undertaken '*so that you can get on with it*' then '*get on with your life*'.

Participants overwhelmingly propose a '*don't worry*' attitude when waiting for results. Similarly they accept the waiting time for '*that's the way it is*'. Persistently when tests are taken after cancer treatment there is no urgency to receive results[60].

Participants describe anticipating '*the big surgery*' should a BRCA1/2 mutation be identified:

> *P3 if it did come back positive I would want a double mastectomy and I would hope that the consultant would agree.*

Treatment options can be identified by participants and health care professionals prior to undertaking the genetic test and while waiting for results. However exceptionally the patient will propose extensive surgery prior to genetic testing:

> *P9 I was really relieved when they said they would take off both my breasts because that was a wee bit of my panic that they were going to go 'we're going to do a lumpectomy'.*

Such a response is identified as maximising survival. Additionally it is recognised that planning for a result that confirms a mutation, may enable patients to come to terms with larger surgery.

When participants consider surgery commonly they describe less extensive, breast conserving surgery should no BRCA1/2 mutation be identified. This is understood typically occur when an information seeking coping style is adopted:

> *P3 I was going down the line of just going for the lumpectomy unless it came back the other way (BRCA1/2 mutation identified).*

Similarly when tumour characteristics require a mastectomy (e.g. a large and extensive tumour) participants propose less radical surgery:

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[60] Unusually within this study population '*is it lost*' is a theme that recurs when results have taken several years. However for these participants testing commonly commenced before modern genetic techniques were adopted. Such events are not anticipated in an early genetic test patient group.

> *R16 (if BRCA1/2 mutation not identified) maybe I could have just had one mastectomy and not two mastectomies.*

This opinion is in contrast with the anticipation of '*the big surgery*'. Alternating between coping style and treatment decisions may occur in response to the cancer diagnosis and the impending genetic status result. This response may assist coping when genetic results are received.

Participants indicate that they are advised how long results are estimated to take. Most commonly responses reveal support for the predicted waiting time. More remarkably results are provided before this time:

> *P3 my results came through so quickly … most things come through quickly when they are positive because the tests don't have to go any further … so when they came through very quickly, prior to coming in to get the tests I kind of thought they were positive and so had my sister … so I was even more surprised to see that they were negative.*

Furthermore, a less expected result may amplify the patient's response.

The Impact of Results

When considering treatment in the presence of a BRCA1/2 mutation the dominant theme is '*get in and get it done*'. This opinion relates to bilateral mastectomy and where appropriate immediate reconstructive surgery. Participants advise onco-plastic surgery, for cosmetic and psychological results that '*put you back together*'. The uptake of risk-reducing surgery for the related ovarian cancer risk is similarly viewed with urgency.

Conversely a false sense of security, worry about a false negative result and uncommonly anger are described in relation to the perceived uncertainty of a result that detects no mutation or a genetic variant of uncertain significance:

> *P9 it annoyed me, 'oh for goodness sake get it right' you know 'you either have or you don't' (laughing) … I thought 'oh god, you're putting people through that & then you are still saying after that you still don't know.*

Emotional responses to information that is perceived to be uncertain vary (see Figure 15: Response to Results, page 157) and frequently relate to factors such as prior cancer experience, support, knowledge and coping style. Each of these factors can impact treatment decisions.

The coping style adopted by the patient at the time results are received is understood to influence treatment and risk-reduction decision-making.

Fear of recurrence is reported in relation to treatment choice, breast conserving surgery, when no mutation or a genetic variant of uncertain significance is identified:

> *P11 I still have this fear of not having the whole lot taken away.*

This fear is associated with the false sense of security that participants report. This theme, worry about a false negative result and treatment decision conflict are identified as the dominant reasons that participants, who have results of no mutation or a genetic variant of uncertain significance, choose to undertake extensive surgery:

> *P4 even though my results were negative my mind was made-up before that I wanted to have this double mastectomy and reconstruction.*

Clinically such treatment may not be warranted when genetic status information is provided close to diagnosis.

Within the study population the uptake of risk reducing interventions including prophylactic therapies varies depending on BRCA status: urgent action is commonly taken when BRCA1/2 mutation is identified and participants report less urgent or no action when no mutation is located. Furthermore coping style, assumed at the time, influences whether the patient adopts a more active or passive role in treatment decisions.

A presentation of the Impact of the Test and Results sub-categories and evolving themes follows.

Waiting, Timing & Blood Test

Consistently participants recognise that their BRCA1/2 status will inform treatment decisions and correspondingly they accept the wait for results. The genetic test experiences of this study population are varied and consequently a range of responses are presented[61]. Further details of the time taken from blood sampling to receiving results are provided within the genetic test categories quantitative discussion and are shown in Table 11: Test Category, Result, Times & Treatments (see page 138). For this theme responses have been clustered, correspondingly waiting responses have been presented by test timing category: before or during treatment and after primary breast cancer treatment; thereafter blood test responses (for both categories) follow.

[61] Within the study population the time taken to receive results span a remarkable range, from 2 months to 10 years: 65% (11/17) < 6 months, 70% (12/17) < 1 year, 82% (14/17) < 3 years, 94% (16/17) < 4 years, 100% (17/17) < 10years.

Timing: before or during treatment

Participants describe fast results:

> *P3 When you are going through chemo you just take each day as it comes so yes it was very much in the back of my mind … my results came through so quickly*

During the wait they do not focus on the test or anticipated results. However participants reveal that they prepare for bigger surgery then reconsider treatment choices when the genetic information is received.

Early genetic testing undertaken for the HBOC patient aims to provide results to inform primary breast cancer treatment (surgery). Dominantly within this group participants require neo-adjuvant (pre-surgery) chemotherapy and BRCA1/2 testing is initiated before chemotherapy. Furthermore test results, for these participants, were predominantly available before the anticipated surgery date:

> *R16 just before the chemo was to start … (I) got my test done … it came back positively for the BRCA1 … almost straight away … I had 5 out of the 6 chemos … (the) 5cm tumour had been destroyed, I think they found something like 3mm on the inside (residual tumour)… the rest of it and the margins were safe and I had the mastectomy and partial reconstruction (laughs) … and removed all my lymph nodes and there's been no evidence (cancer) at all*

Participants indicate that pre-surgical chemotherapy to reduce the tumour provides an ideal opportunity for genetic testing to inform treatment. They identify that the available time can be used to consider the genetic test results and identify appropriate surgery including, when a BRCA1/2 mutation is identified, prophylactic surgery.

Exceptionally waiting time exceeds the expected time that is advised by clinical genetics:

R15 I kept asking 'any results?'… at least a year before I even got a letter…believe it or not it was ten years, almost to the day … finally got a letter from them saying that I had (BRCA).

This testing commenced before current genetic techniques and the wait for results is prolonged. Nevertheless this is an exceptional situation and results were received 7 years after the 3 year anticipated time. The response to the BRCA mutation result is justifiably more remarkable:

R15 I was quite upset when I got that (BRCA result) because … over ten years I was getting the odd letter saying they can't find anything I have to say that it was a shock to be told that.

For this participant the impact of the wait did not have any effect on cancer treatment or prophylaxis, decisions were based on predicted genetic risk. When results were received they confirmed the treatments that had been undertaken.

Timing: after treatment

The wait for results is not viewed with great significance by the population who undertook testing after primary cancer treatment. Consistently this population require BRCA1/2 status to inform risk-reduction interventions. Urgency is not a theme:

P1 it was going to take a while … a couple of months. I just kind of forgot about it, it's going to take however long it's going to take, there is no point in … worrying about it.

Similar to participants undertaking the test before or during treatment, participants do not focus on the test or anticipated results:

P6 there's no (not) really much you can do until … (you) get told whether (pause) you've got it or not.

While waiting for results the theme of '*not much you can do*' expands for these participants; they do not anticipate or plan for prophylactic interventions.

Frustration over the wait is occasionally communicated:

P11 wait 3 months for genetics … wasn't fantastic, that's the way it was.

The participant does not place great significance on, and accepts, the wait. It is anticipated that the current 3 week turnaround time would have a lesser impact.

Within the study population participants describe concern that their sample or results are lost:

P10 'did they loose it?' … 'I wonder what the lab is doing with that sample?'

Notably this participant was required to provide a subsequent sample for further investigation. Testing commenced in 2001 and results were provided 4 years after the initial sample. It is anticipated that modern techniques ensure that results are available today within significantly less time and that such an experience will not occur when undertaking BRCA1/2 testing to inform treatment.

The Blood Test

The blood testing element of the test is overwhelmingly viewed, by participants, as acceptable. Consistently the women gave little regard to the blood sample and made light of the blood-test procedure:

P1 'YES! Just take it!' (laughing) … you have had so many needles in you what's another thing of blood.

Less commonly among the study population, when BRCA1/2 testing occurred before or during treatment, participants described issues with sample timing, for example to ensure that chemotherapy does not affect the genetic quality of the blood sample:

R15 they said they had to take it before the chemo, cause the chemo would damage … DNA.

For this study population the genetic testing occurred most commonly after initial cancer treatment.

Exceptionally an unexpected strong emotional response may be communicated where the blood taking process triggered the release of an overwhelming feeling of responsibility for self and family:

> *P10 It's quite a responsibility … I remember crying, I wasn't expecting to be doing that, I don't really do that.*

Responsibility is a theme that recurs throughout the data, in this dialogue the cancer-risk implication related to the test may be accredited to this reaction. Additionally it can be anticipated that this responsibility extends to family cancer-risk.

Treatment decisions

Participant experiences, results and opinions varied. However BRCA1/2 status is identified as having the greatest impact on treatment decisions, therefore responses are categorised by test result and not timing of the test. It is similarly anticipated that a future HBOC patient population undertaking early testing treatment will be most influenced by BRCA1/2 result. Treatments undertaken are detailed on Table 11: Test Category, Result, Times & Treatments (see page 138).

No mutation or BRCA1/2 variant of uncertain significance

The impact of test results for this population are divided by primary cancer treatment and prophylactic treatment responses.

Primary cancer

Dialogue reinforces the primary reason for undertaking genetic testing:

> *P4 'will I have new options now I'm getting the testing?'… 'what will they do?'*

Bespoke treatment options, including prophylactic interventions, with the goal of maximising survival are emphasised as the dominant reason that participants undertake the test.

Within the population response to results are divided. BRCA1/2 test results overwhelmingly inform treatment choice:

> *P3 the decision … to do a lumpectomy … the only change it would have been is if it had come back positive. I would go along exactly with what they think. They are qualified they have the expertise, I don't. So there was no real discussion afterwards because to me it was black or white. If it came back positive I'm going down one route (mastectomy) and if it came back negative I would go down the other route (breast conserving surgery).*

The coping style that the patient adopts when treatment decisions are made is identified as a significant factor affecting the process. Within this dialogue an information seeking style is identified: a passive role is adopted, the patient defers treatment decision-making to the surgeon. The initial surgical decision was based on tumour characteristics, subsequently the genetic result confirms appropriateness of the procedure.

Conversely participants chose to continue with treatment decisions that were established before genetic information is available:

> *P9 I said 'can I have a double mastectomy?' … (surgeon) 'absolutely and in that case you can have a, we can do an immediate reconstruction', so that was so that was the decision*

While testing, proposed by the surgeon, is undertaken during treatment the surgical decision is taken before results are available. Maximising survival is identified as a significant factor in the treatment decision:

> *P9 cut whatever bits off me that you could … just as long as it meant that my odds were better and it did, they said it was 80% … decreased my chances by 80% of anything recurring*

A false sense of security is not identified within the dialogue, the decision was made before genetic results were available. This participant's coping style is less clear; an avoiding style is evident when treatment is initially proposed (by the patient) then an information seeking style is adopted when deferring to the surgeon's proposal.

Similarly (and based on timing of the test) participants chose to continue with treatment decisions that were established before genetic information was available:

> *P4 even though my results were negative… my mind was made-up before that … if they had offered me it (double mastectomy and reconstruction) I would have just took it … even without any genetic testing … it was always at the back of my mind … it was a grade 3.*

An avoiding coping style is identified in this dialogue; an active role in the treatment decision is adopted.

Commonly within dialogue relating to no mutation, treatment decision is based on tumour characteristics and not established genetic risk.

> P4 I'm still guessing I've got some genetic link. I guess I'm in that category but what that actually means to me and will it come back?

A false sense of security and disbelief are identified as significant factors in the response. While this treatment choice is made before receiving the result (that identifies no mutation) the reaction impacts subsequent cancer risk-reduction decisions.

Prophylactic treatments

Contrasting the overwhelming opinion is that additional prophylactic surgeries would be considered should a mutation be identified:

> *P6 gettin' (getting) your breasts off, that's a bit radical, but if they said 'yeah, you had the high (risk)' well then you would really have to consider (it).*

More definitively surgery would be undertaken:

> *P5 (BRCA mutation identified) then I would have definitely gone and done it … make it clear cut for me to have my surgery … at higher risk and had to get it done or maybe I could leave it a little bit longer till I'd finished all treatment.*

The genetic result provides context and a timeframe for undertaking risk reduction interventions. An information seeking coping style is displayed; the participant is being guided or taking a more passive role in the treatment choice. Conversely in the presence of a confirmed BRCA mutation prophylactic treatment is undertaken rapidly.

Within the data exceptions occur. In one such situation genetic testing occurs in response to a third cancer. Previous breast and ovarian cancer indicated a potential HBOC:

> *P8 I never thought it would have happened the second time … (if tested the) first time they would be looking into my genealogy … say I did have the faulty gene, it would have been discovered earlier …that would have … cleared things up… you could get on with the procedure*.

The dialogue indicates that early genetic testing, would have informed primary cancer and prophylactic treatment, thus preventing recurrence and the impact of additional surgery and cancer treatments. These are reasons identified throughout the study dialogue as important motivators for undertaking early genetic testing; this example reinforces the rationale.

Recurrently participants propose undertaking prophylactic ovarian surgery before genetic status is confirmed:

> *P9 I would have had my ovaries removed … (doctor) explained the chances of ovarian cancer would be heavy*

Where results do not identify a mutation:

> *P9 it took away the option of having to think 'do I go through another operation?'*

Genetic status personalises prophylactic treatment decisions.

BRCA1/2 mutation identified

Test results responses for this population are divided into primary treatment and prophylactic treatment.

Primary cancer

Women undertaking BRCA1/2 testing to inform primary cancer treatment use the BRCA1/2 test result to inform their surgery:

> *R16 maybe I could have gone away and just had one mastectomy and not two mastectomies.*

The result provides a clear genetic risk which assist initial treatment decisions:

> *R16 I had confirmation of my BRCA1 and I had to have my two mastectomies.*

With a confirmed BRCA1/2 mutation cancer treatment and prophylactic therapy are undertaken at the same time to reduce the need for further interventions:

> *R16 At the end of the day it's preventing you from getting cancer … so get in and get it done … from a prophylactic side of things, if you can achieve what …the plastic surgeons can do, I've dealt with it, they take you apart (laughs) but they can put you together…it's a no brainer.*

Additionally breast reconstruction cosmetic results are presented in support of immediate bilateral reconstruction.

Prophylactic treatments

The genetic result is commonly viewed as confirmation that appropriate treatment has been undertaken and that no additional risk reducing intervention is required:

> *R14 I knew that (because of) the family history, it would be a recurrent cancer, the best thing to do was to eliminate it completely … just get them both taken off at one time…double mastectomy with bilateral implant(s).*

Similarly for the population with an identified mutation support for bilateral mastectomy is consistent:

> *R2 the thought of going through an operation, going through all that treatment, getting out of that and then developing another breast lump and having to start again … I wanted to get on with my life.*

Participants overwhelmingly promote extensive surgery, including reconstruction, based on the aim of reducing risk, avoiding further cancer and treatments. Consistently concern about the link between breast and ovarian cancer this is presented as a significant factor in undertaking BRCA1/2 gene testing. BRCA1/2 status is identified as having the greatest impact on ovarian prophylactic treatment choice. Correspondingly responses have been categorised by test result (and not timing of the test). It is similarly anticipated that a future HBOC patient population undertaking early testing treatment will be guided by their BRCA1/2 result.

Recurring throughout the study population, participants had previously undertaken ovarian surgery before their BRCA1/2 status was established:

> *R11 as a precaution like with my aunty having ovarian cancer… I already had hysterectomy (and oophorectomy) when I went to get results (genetic test).*

Such decisions are commonly based on family history risk prediction calculations. Comparably but conversely participants describe needing to know their BRCA1/2 status prior to making an ovarian surgical decision. Where a mutation is identified:

> *R14 (I) had to decide whether to have my ovaries taken out because of the genetic strain … so I decided to do that as well and get my ovaries taken out about 3 months (after genetic test result).*

For a younger participant with a BRCA1/2 mutation the decision for oophorectomy is less straightforward:

R16 we made a decision between us (patient and surgeon) that I was still at a reasonably low risk and if I wanted to I could go away, have children and then I could come back and reassess it in due course.

Additional considerations for younger patients relate to childrearing decisions and an early onset menopause with the associated medical risks:

R2 without having the results of the test it was difficult to get the gynaecology department to agree to it because of my young age … he wasn't keen to do the hysterectomy and remove the ovaries because of my you age … I was able to go along to him and say I've got this faulty gene with a high risk of me developing ovarian cancer … even I still had to fight with him a bit, cause he wasn't keen to do it but I just had to dig my heels in and insist, and so he agreed to do it

This participant portrays surprise, the BRCA1/2 mutation was not sufficient and further discussion was required for ovarian prophylactic surgical intervention.

8.6 Hereditary Cancer

While dialogue relating to hereditary cancer does not relate specifically to treatment choice it is considered relevant to patient experience. Furthermore patient acceptance is identified as a significant factor that will influence the uptake of early BRCA1/2 testing. Closely associated, awareness is identified as a factor influencing the uptake of genetic testing and personalised treatment decisions. It is relevant to present patient experience and opinions to assist in the identification of plausible and acceptable approaches to improving the management of breast cancer, through early genetic testing.

Key Findings: Hereditary Cancer

Most commonly within the study population participants have an established hereditary breast and ovarian cancer history. These women attended FHBCC prior to their diagnosis and have established a rapport with key members of the breast MDT. This relationship is identified as aiding their decision to undertake genetic testing. Additionally the family experience of '*growing u*p' with cancer and attending FHBCC provides breast cancer information that a patient with an unestablished history is unlikely to access. Correspondingly participants with significant family history indicate a high acceptance of early genetic testing.

Less often family history is identified after breast cancer diagnosis. Within the study population where family history is not established tumour characteristics or a young age at diagnosis can trigger a genetic referral. For these women in the study population BRA1/2 testing is more commonly offered later in the cancer journey and not at diagnosis. However they appreciate and support the relevance of testing.

Coping style is identified as influencing whether the patient or healthcare professional will initiate a genetic test discussion and timing of the test. For example, participants who adopt an information seeking coping style at diagnosis are found to request genetic testing while those with an avoiding style will more commonly accept a test proposal.

Participants describe health behaviours that are adopted to reduce cancer risk and improve prognosis. However they describe questioning the impact of these at diagnosis and when a mutation is identified. Genetic counselling could be used to reinforce the effect of positive health behaviours for women with BRCA and non-BRCA HBOC.

Awareness

Participants communicate a diverse range of HBOC knowledge. Commonly they identify age as a significant HBOC risk factor. Associated with this they anticipate that a younger patient population will obtain maximum benefit early genetic testing. The maximising survival theme recurs throughout dialogue relating to this opinion.

Most commonly within the study population a test reveals no mutation or a mutation of uncertain significance. These participants have consented to future BRCA1/2 re-testing. While this process is overwhelmingly supported it may reinforce the false sense of security or disbelief when a test does not identify a mutation. Furthermore participants indicate they would gain reassurance should a mutation be identified with re-testing.

Patient Preferences

Participants overwhelmingly favour face-to-face discussion when early genetic testing is proposed. Additionally written information is identified; participants consider that supplementary material that reinforces the purpose and benefit of early testing. Written information can assist their decision to undertake early genetic testing:

> *P8 face-to-face is a good idea …. also writing … sit & ponder … re-read it … weigh up 'is it too much to take in all at once?'*

Furthermore participants identify that relevant healthcare professionals require BRCA1/2 gene and early genetic test knowledge.

A presentation of the Hereditary Cancer sub-categories and evolving themes follows.

Family history

Established family history

Within the population family history HBOC details are commonly established prior to breast cancer diagnosis[62]:

> *P9 (breast cancer) my mums sister, my grandmother and 2 of her daughters and then 2 of my mum's daughters… my sister having cancer… and then (I) you have got breast cancer … one sister's had twice, two primary breast cancers, 10 years apart… had lumpectomy …10 years*

[62] In such cases patients will usually receive specialist breast care and surveillance through the NHS Tayside FHBCC. Furthermore FHBCC patients are exposed to knowledge of their family breast cancer history and individual breast cancer risk (calculated using Clinical Genetics techniques). A typical FHBCC pedigree will identify a significant number of first and second degree relatives with breast or ovarian cancer, including cancer recurrences.

> *later double mastectomy… mother bowel cancer, father lung cancer, grandmother had breast removed 1920s or 30s…quite a history in my family … from my mother, 8 half-sisters all in the same line, a lot of women in the family.*

Participants who report significant family history indicate a high acceptance of early genetic testing. Correspondingly the uptake of early genetic testing to inform treatment should be anticipated to be high, where families have an extensive history. Participants report greater urgency for genetic testing when they have a significant family cancer experience. BRCA1/2 status knowledge for the family is suggested as a significant secondary factor in such patient's undertaking testing.

Previously unestablished family history

Less common within the population are participants who are unaware of the extent or relevance of their family history until their cancer diagnosis. They report that family history of breast or ovarian cancer may be recent and involve few relatives. For women with a previously unestablished family history, participants indicate that knowledge and acceptance of HBOC and increased breast cancer risk may be poorer than those from families where history is expansive and women have '*grown-up*' with cancer.

A young diagnosis (age 45) and triple negative tumour can trigger genetic enquiry.

> *P3 I was diagnosed … with triple negative breast cancer … it's 3 crosses … I have no family history on one side because my mother was adopted so you always kind of look down the negative thoughts and think well maybe there is something there.*

This dialogue, whilst atypical in the study data, identifies both a triple negative tumour and an unestablished family history. Significantly an information seeking coping style is evident:

P3 after a bit of research I realised that if it was genetic … it would be more suitable to have a double mastectomy … I've always thought about genetics … my husband's side of the family is riddled with breast cancer.

Furthermore family history cancer experience is identified as a major factor influencing this patient's search for information and decision to seek genetic testing. It is however exceptional and atypical that this family history experience and knowledge are from an unrelated bloodline. Nevertheless for this participant, triple negative tumour characteristics together with an information seeking coping style ensured that early genetic testing was undertaken. Based on this patient experience, it is anticipated, that a patient who adopts an avoiding coping style at diagnosis, would not be offered early genetic testing. Rather, testing would be proposed later in the cancer journey:

P3 at that point I spoke about genetics and they said … that it would be looked at after all my … treatment.

In contrast with this assumption, another participant (P12) with a triple negative tumour, and little family history (1 aunt diagnosed 6 months earlier), was offered genetic testing by the FHBCC breast surgeon. Genetic counselling occurred however testing was deferred until primary cancer treatment was completed:

P12 (at diagnosis) I don't really think that I thought about the gene side of it … at that time because I was more concerned about whether I was getting to keep my breast or not … that was my main concern.

An avoiding coping style has been identified throughout dialogue relating to diagnosis and the treatment decision; while the patient does not seek additional genetic information they assume an active role in the treatment decision. However had a BRCA1/2 fault been identified dialogue indicates an information seeking style; dialogue implies adoption of a passive role should risk reduction intervention be required. These dialogue (P12) exemplify movement between coping styles:

P12 I would have done whatever they said, if they advised me 'this is what you need to do' I would have done it, you know you don't want to put your life at risk.

Exceptionally this participant would have undertaken additional interventions rather than favouring a combined approach, as is overwhelmingly favoured by the study population.

Access screening?

Overwhelmingly participants are aware of HBOC prior to their cancer diagnosis and FHBCC screening is commonly undertaken regardless of genetic test result. These participants report attending FHBCC for screening every 12-24 months depending on risk[63]. Consistently participants describe relief that they attend screening:

R16 I've been visiting the family history clinic for a number of years …from my early 20's… I have my annual check at the family history clinic.

Patients attending annual FHBCC report forming supportive relationships with the clinical teams who provide HBOC care. These relationships are considered important and for participants this supports their decision to undertake genetic testing and subsequent treatment decisions.

Health Behaviours

Risk-reducing health behaviours are presented in relation to diagnosis although in this study, seldom affect treatment interventions. Where no mutation is identified:

P2 I am healthy, you know (not) drinking too much alcohol, eating rubbish, not taking exercise I eat all my five or more my six portions of fruit and veg every day.

[63] This comprises of a review by Breast Specialist (Surgical or Medical Doctor), breast examination then dependent on age and risk mammography.

A negative BRCA1/2 result can leave the individual questioning why they have cancer. Correspondingly where a mutation is identified similar reference is made to health behaviours and risk:

> *R15 it never came as a shock … I breastfed and I always played a lot of sport, I wasn't overweight … I don't really drink much, I've not ever been a drinker.*

While an extensive family history is identified as the most significant cancer-risk factor, positive health behaviours have been adopted in an attempt to reduce cancer risk. Participants acknowledge the impact of healthy behaviours in association with risk and improving prognosis:

> *R16 I was dealing with the cancer side of things, I was going for the (neo-adjuvant chemotherapy, mastectomy, radiotherapy and prophylactic mastectomy), I was doing everything I could possibly do. You know I drink very limitedly, I'm not a complete nutter, I have the occasional, don't get me wrong but I look after myself, I eat well, I do all the right things … I've never smoked, maybe I won't get it (recurrence). I've always been doing my bit to keep myself healthy, which wasn't obviously enough but maybe it was enough to cure me and to stop it from going further, I don't know.*

It may be anticipated from this dialogue that genetic counselling can reinforce positive health behaviours, to reduce risk and improve prognosis.

Genetic Knowledge

Within the dialogue a range of responses relating to genetic, health and scientific knowledge are presented. Knowledge is revealed as a factor that affects the uptake of genetic testing and treatment choices. Patient knowledge has been obtained from a variety of sources; participants indicate FHBCC, their (and family member's) occupation, the press and internet.

Participants propose that the uptake of early genetic testing can be anticipated to be higher for a younger patients:

> *P10 for younger people it is worse for if they get a cancer, it could be fast growing kind … I know from 50 downwards you are of a higher risk of recurrence and also of genetic.*

Treatment decisions may be influenced by patient knowledge:

> *P9 (scientific community) you know a lot about what you know but there is an awful lot more that … even with the knowledge it is not guaranteed that you are going to develop (breast cancer)*

This knowledge may contribute to this participant's false sense of security that is indicated in response to a result that identified no BRCA mutation.

Health care professionals

Less often participants describe experiences that reveal genetic knowledge gaps within their health care team:

> *P12 the nurses that looked after myself didn't really discuss anything about genetics. I did say to the nurse mine was triple negative, she was like 'oh, oh right', she didn't really discuss it and didn't really know much about it … it would be good from their point of view and the patients to know more about genetics (nurse education).*

This uncommon dialogue highlights patient recognition of a need for genetic education. They indicate that where health care professionals are not informed the uptake of testing and treatment decisions may be compromised.

Re-testing

Future re-testing is relevant for participant's whose test identifies no mutation or a mutation of uncertain significance. Participants were asked if they had knowledge

that their sample would be retested. Overwhelmingly participants confirmed that they were aware and happy for future re-examination.

> *P2 things are changing all the time … they are storing the results and all (sample) … it's fine, I'm quite happy about that.*

The dialogue indicates an appreciation of future scientific progress that may subsequently reveal a genetic mutation. Similarly participants anticipate that a mutation will be identified:

> *P9 I think you will find something else … … I hope I am still in their files so that if anything pops up then I'll be informed.*
>
> *P12 I would be quite relieved actually … the not knowing 'is it genetic or just something that happened?' ... 'oh yeah we've found a gene' … I'd be quite relieved actually.*

The dialogue, a response to results that do not identify a BRCA1/2 mutation, provides further evidence of a false sense of security or belief that the results are a false negative. While risk-reducing interventions may be required should a subsequent BRCA1/2 fault be identified participants indicate support for such intervention should it be required, at a later date.

Patient Information

Based on their genetic test experiences the study population propose a range of methods for disseminating information about the option for early genetic testing to inform treatment. Two broad groups were identified: discussions and written information.

Face-to-face discussions

Consistently face-to-face discussions are favoured by participants both for the initial proposal of early genetic testing and when providing extra information.

P3 appointments ... so informative, so helpful for both my husband and I.

The proposal should include:

P5 an explanation of why things are done, the time scales, having test would help decide what you get done, explaining it properly from the outset.

However caution is advised:

P8 face-to-face is a good idea … if not too mentally disturbed from (diagnosis).

A recurring theme is whether people want to know their BRCA1/2 status:

P9 some people don't want to know … hugely individual.

Contrastingly and based on experiences with other patients:

R2 depend on the person's nature … people that I've gotten to know through Macmillan and going through treatments … people who wanted knowledge and wanted to know what was going on … probably more to do with personalities and way they cope rather than knowledge ... they wanted to know every little bit of detail, what word meant, looking everything up … I can see them benefiting from it (genetic test).

Coping style should be anticipated as an important factor in the uptake of early genetic testing.

Participants additionally identify long periods of time where they propose that genetic testing can be discussed, this is particularly relevant for patients undertaking neo-adjuvant chemotherapy:

P1 you can be there all day … talking to a nurse in a room while you are getting the drip in

Participants indicate that such times can be anticipated as useful, for sharing extra information that will assist the patient to decide whether to undertake early genetic testing. Although it has been (P12) previously indicated that staff training will be required to ensure equality of information.

Written Information: Leaflets, The Internet & Results Letters

Supplementary written information is proposed assist decisions about early genetic testing:

> *P8 also writing because you can sit and ponder a letter, you can re-read … you've got to weigh up … too much to take in all at once.*

Less frequently the function of providing information for the family while undertaking testing is described as an important role:

> *R11 You think 'I have to take all this information in' … when I go back home all the family is going to be asking ... you've got to have some sort of answers or something about what's going to be happening.*

Participants indicate that written information would assist where patients wish to discuss the option for genetic testing and the impact that BRCA1/2 results have on treatment decisions.

A contrasting opinion that relates to the proposal for early genetic testing:

> *P1 (at diagnosis) giving them a leaflet at that time … you can put it in your pile of stuff to read at some time and think about when you have read. … (during neo-adjuvant chemotherapy treatment) a leaflet or anything when you are sitting having chemo, cause you are sitting for some considerable time.*

This participant later indicates that such a proposal would require follow-up to ensure that the patient is aware of the relevance of early genetic testing and the impact that it can have on their treatment plan.

The internet is presented as a significant source of genetic information:

> *P12 I did go looking for information, there is so much on the internet (och sound) 'I don't really understand' … most of it, you didn't really know where to start looking, I abandoned the search at that point … the internet there is just so much and it frightens you … find stuff on it, it makes you worse … if you don't have information that is the first thing that you do, you go to*

the internet and that's a nightmare, it's really scary (laugh) (other people's experiences) some are quite bad, you are thinking 'is that going to happen to me?

Participants recognise that caution is required, and that patients should be advised where to seek appropriate information. They indicate that when sufficient information is provided at the outset, this can guide and inform patient decisions relating to early genetic testing and treatment.

Participants universally support the use a letter, subsequent to face-to-face genetic counselling, to confirm genetic test results:

P12 the letter was really useful because it explained the findings and also explained that although they hadn't found anything, that there were more genes that they were looking for. P3 it was brilliant, pitched at the right level … understood it fully.

Associated with the proposal for early genetic testing, participants recognise that appropriate systems and documentation will be required to assist the process for all involved.

8.7 Early Genetic Test

Within the population a range of genetic testing experiences exist. Details are provided in Table 11: Test Category, Result, Times & Treatments (see page 138) and throughout the study results[64]. Specific data relating to participant experience of early genetic testing to inform treatment are found within the previous section[65]. Where an early genetic testing experience is not available the participant's dialogue is either unguided or where required prompted by the use of hypothetical questions that provide an offer of testing at or close to diagnosis, with results available within 3 weeks to inform treatment.

Key Findings: Early Genetic Test

Based on a hereditary breast cancer diagnosis and personal genetic testing experience, participants overwhelmingly indicate their support for early genetic testing to inform treatment decisions, for the newly diagnosed HBOC patient. Significant satisfaction and benefit is reported by participants, they favour having '*genetics to back you up*' to help choose the right treatment. While all participants support early testing those who undertook early genetic testing to inform their primary cancer treatment indicate the highest levels of support.

Dominant themes that relate to patient satisfaction, following the provision of early BRCA1/2 testing to inform '*tailored treatment*' or prophylactic decisions. Participants describe that '*it makes sense*' to '*have it done*' early to gain personalised genetic information for risk-based treatment decisions with the ultimate goal of '*tailoring*

[64] Most relevant are Sections 8.4 Genetic Testing and 8.5 Test Results.
[65] Section 8.4 Genetic Testing: Inform Treatment?

treatment' and maximising survival. Coping style is identified as a factor that impacts test and treatment decisions. Nevertheless participants indicate that treatment decisions will be informed by early BRCA1/2 testing.

Urgency is a recurring theme; participants seek and require genetic information quickly. However genetic information is considered to be something that '*you don't want*' but '*need to know*'. Participants state that there is '*not really a good time*' to discuss early genetic testing and propose that testing should be '*part of the package*', integral with diagnosis and treatment planning. A '*get it over wit*h' opinion is consistently voiced by participants; they support an early test proposal and subsequent BRCA1/2 testing at diagnosis or as soon as possible. Nevertheless it is recognised by participants, that for some, diagnosis can bring too much information, '*all things you don't know about*' and emotional overload. Participants identify that early testing may not be suitable or appropriate for all patients. However they favour patient choice; an early proposal for testing and allowing the patient to undertake testing when they are ready. Furthermore they state that the proposal should clearly indicate the benefit of early personal genetic risk information to inform treatment. Consistently participants report that treatment can be personalised at primary intervention or later if risk-reducing interventions are required.

Participants identify that the offer of early genetic testing will be best received when a knowledgeable member of the genetics team makes the proposal and is available to promptly respond to questions. This will ensure that the decision to undertake testing does not delay primary cancer treatment. Furthermore this may have additional relevance where family history is not established at the time of diagnosis.

When early testing is indicated participants propose, that a clear timescale, specifying the wait for results, is required by the patient. While the potential 3 week wait for results is consistently viewed with little consequence participants indicate that this timescale should, for each patient, be approved by the surgeon; importantly they state that testing should not delay treatment. However where concerns exist participants indicate that intervention planning with '*pencilling-in*' for big surgery could prevent any treatment delay. They propose that the scheduled surgical plan can subsequently be altered when the final treatment decision, informed by genetic status, is taken.

Participants propose that waiting for genetic results can occur during the time between diagnosis and treatment. They describe that this as a busy time; when commonly patients start coming to terms with their cancer diagnosis, attend treatment-planning appointments and arrange support to assist the family to during their cancer treatment.

Within dialogue relating to early genetic testing participants provide additional reasons and rationale for undertaking an early test; these fit with the maximising survival theme. Furthermore it is identified that fear of recurrence is a significant factor motivating support and uptake of an early test. Significantly participants indicate that a younger patient population should be anticipated to gain the greatest benefit from an early genetic test. This finding may relate to the study population experience, where commonly diagnosis occurred between the ages of 37 and 50 years. Similarly participants predict maximum psychosocial benefit, for younger

patients, when immediate reconstructive procedures are undertaken should mastectomy be indicated.

A presentation of the Early Genetic Testing sub-categories and evolving themes follows.

Inform treatment

Participants indicate that early genetic information, close to diagnosis, is essential for the high risk HBOC patient:

> *R14 it's something you have to do, it's not something that you want to do.*

The results provide personalised risk information:

> *P1 you are better to know what is going on.*

Early BRCA1/2 results bring clarity and inform appropriate risk-based treatment decisions:

> *P10 if it was all done at the beginning then it would be like 'well this is what I'm doing'… I would have gone with it … I wouldn't mmm hesitate at all … you should do it sooner, than later … you might not need to have a mastectomy because of that (result) … without all the information how do you know that you have had the right thing done.*

Participants recognise that treatment options are associated with improvements and personalised care:

> *P5 I would want to know everything … to help make a decision … (it's) got to be a good thing, having the choices.*

Within the population an event recurs; proposed surgical procedures based upon predicted risk, using genetic / family tree risk predictions:

P11 the decision (surgeon)… their thoughts were always to do a lumpectomy.

However participants indicate that patients do not always endorse a proposed plan and indicate undertaking more extensive surgery to maximise survival. Coping style adopted at the time of diagnosis is identified as a factor can impact whether a test is proposed by the patient or healthcare professional:

P9 If I needed genetics to back me up … push my case to have both my boobs removed then yes I would want them in the room.

Survival factors that motivate the preference for mastectomy include family breast cancer experience (and treatments) and dependent children:

P11 high risk (family history) … *my mother when she was … early 40s had a mastectomy for breast cancer. My sister 3 years previously had the same diagnosis … exactly the same* ages … *my children were 4 and 2, I was in my 40s … my priority was staying alive as long as I possibly could*.

While patient preference may be based upon coping style and psychosocial response the surgeon can agree to perform extensive surgeries, such as bilateral mastectomies. However:

P11 I was quite disappointed when she said they would 'if that's what you want to do fine, but we wouldn't certainly recommend it from a genetic point of view' (surgeon)

This exceptional narrative indicates that the patient expected to be challenged about her preferred surgical choice. The recommendation to undertake BRCA1/2 genetic testing was proposed by the surgeon in response to this discussion and subsequently the participant undertook breast conserving treatment based on her personal genetic risk.

Participants indicate that treatment will be altered in response to genetic information, and when no BRCA1/2 mutation is identified surgery can incorporate less extensive procedures:

> *P4 if it had come back negative at that point (pause) … it would help me make up my mind and no there wasn't a family (genetic link), get the lump out (lumpectomy) … I probably wouldn't have considered it (double mastectomy)… if you'd tested me at that point I might have looked at my options differently.*

While the dialogue indicates that the participant undertook genetic testing after cancer treatment, support for early BRCA1/2 information to inform treatment is evident.

Conversely and overwhelmingly participants identify that in response to the genetic test they prepare for a BRCA1/2 mutation:

> *P3 unless it came back the other way… that would advise you (imaginary person) to having the prophylactic surgery as well as the mastectomy*

Larger surgical procedures including prophylactic treatment, either at the time or shortly after their cancer treatment, is advocated by participants, when a BRCA1/2 mutation is identified:

> P10 *(slowly) if it is a high risk I think you would go along with it (bilateral mastectomy) 'cause why would you want to be living with the thought that you know, it could recur… if you had had the testing and it was yeah (BRCA mutation identified)… probably would have gone (quietly) (for prophylactic surgery).*

While the dialogue relates to a hypothetical question the participant exposes an information seeking coping style. Correspondingly coping style can be anticipated as a factor that will impact treatment choices when early testing is provided. An alternative response may be expected where patients adopt an avoiding style; a less accepting and a more active role can be assumed.

Participants indicate that results will alter treatment decisions, particularly when extensive surgery is anticipated:

P3 the people that were thinking … of taking everything away, the big surgery, might be persuaded to then have the lumpectomy if you found out it wasn't the BRCA genes, yes I think these people would be more likely to change their mind.

This dialogue proposes that HBOC women who adopt an avoiding coping style, and are active in treatment decision-making, may gain most benefit from early genetic testing.

More extensive and / or risk-reducing prophylactic surgery that is indicated when a BRCA1/2 mutation is identified may nevertheless present a difficult decision:

P7 having my other breast removed, I think I would have done that … it would be a very hard decision I mean I honestly feel, even at this stage of my life … I am sure I would … I just put so much stock on my family, I just want to be there for them … I think even if they said to me.

However a recurring theme is the need to minimise risk and the number of procedures that are required:

P8 save (your) body having to go through it (cancer and treatment) a second time…harder it is for (the) body each time to recover, some of us have a very bad time

The survival theme prevails when prophylactic treatment decisions are required:

P9 some women have a huge problem with having their breast removed … seriously was a no brainer for me … I would have had my other breast removed because I want to give myself the best chance. I would have had my ovaries removed.

P6 people should get tested earlier … doctor said 'this is the best option fur (for) ye' (you)… then you would go, I would go with the advice… of the doctor (mastectomy), you can always get (pause) reconstruction (quiet).

Cosmetic results will be considered when reconstructive surgery is appropriate:

P9 if they hadn't given me immediate reconstruction I don't know that I would have even come in for reconstruction … I love the way mine worked and the way it has all gone, it is fabulous.

However the physical and psychosocial impact of large reconstructive surgery is acknowledged:

> *P9 big surgeries… truly don't know that I would have come back for reconstructions. I don't know that I'd have come back … such a huge thing for my kids, for my husband, for my life.*

This dialogue further supports the theme of minimising or combining procedures.

Await results

Commonly participants consider that the 3 week guideline time for early genetic test results is acceptable. Opinions fall into two broad categories: Overwhelming support and Concern. Notably, within dialogue that supports the 3 week wait for results, participants reinforce the main reasons for undertaking the test and present new rationale.

When a 3 week wait for results is presented with an early genetic test proposal, overwhelming support is demonstrated, dialogue includes:

> *P3 perfect, P7 marvellous, P10 oh, wow!* and *R15 wonderful … great, super.*

Waiting 3 weeks after diagnosis, and the genetic blood sample, is regarded with little consequence and as a short time:

> *P8 I don't think that would endanger your life …waiting such a little time.*
>
> *P12 I would think in the life of cancer three weeks is not going to make much difference.*

Participants acknowledge that patients experienced period of waiting between diagnosis and primary treatment:

> P11 *that would be acceptable completely … I don't think it is too long because (pause) you know between your diagnosis and your chemo you have got to wait anyway so I don't, I mean 3 weeks is not really a long time to wait, so I don't think it would be that much of a problem.*

This time is described as eventful; with appointments for treatment planning and arrangements for assisting the family to cope during their cancer treatment:

> *P10 a busy time, getting all these things done (tests) … my feet just didn't touch the ground at that time, which wasn't a bad thing. You didn't get time to really think too much about things.*

It is also recognised by participants that coming to terms with a cancer diagnosis and interventions takes time:

> *P10 I don't think that is too bad, you need some time.*

They propose that this emotional process can start in the time between diagnosis and results.

The dominant opinion is that the benefit of personalised treatment outweighs any concern about a 3 week wait for results[66]:

> *P1 I think probably the wait probably outweighs … it is probably beneficial …I think probably it is worth waiting the three weeks.*
>
> *P12 if it is going to be a better outcome then it might be worth it.*

However it is acknowledged that individuals will view the 3 wait for results differently:

> *P7 it depends on the person … I honestly feel it would be up to the person themselves.*

Less commonly participants identify that, for some patients, any wait may create distress:

> *P6 3 weeks is a long time (laughing) isn't it when you're worrying.*

Urgency for treatment is a recurring theme and concern regarding a 3 week wait is supported by more exceptional experiences:

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[66] Reinforcement of the theme '*getting the right treatment*' consistently recurs when participants justify the 3 week wait:

> *P3 it would have been very hard having a lumpectomy and then being told that it was genetic … a positive BRCA gene because then to make the decision to go back again.*

Additionally avoiding unnecessary and extra surgical procedures is commonly described is support of the wait:

> *P12 you could end up with surgery that you don't really need to have if you had surgery and then said 'oh you've got the high risk gene' and then you would have to go back and have more surgery.*

P9 (3 week wait) I think that would be too long (quietly)… I was wanting to wait and have a week (holiday) but they just said 'no' … 'we want to turn this around as quickly as we can' … huge urgency… I was advised against doing it (postponing surgery)… huge hours in theatre were booked in well in advance … guess there is always an urgency

Nevertheless the 3 week wait potentially delaying primary cancer treatment is a concern. Participants commonly indicate that treatment should start immediately after diagnosis:

P5 (emphasis) I was just desperate to get started … I don't think I'd want to be delayed.

R15 once you know you have cancer you want treatment straight away …it's not something you want to put off at all … I came home from (holiday) two weeks early, I just feel that if you know you have cancer you don't want things delayed … I would think that most people would think that.

Participants anticipate that treatment planning should 'pencil-in' procedures:

P9 maybe book their theatre (for bigger surgery then) reduce it.

Thereafter when genetic information is available they indicate that the treatment plan should be finalised, with no delay:

P5 I don't think I'd want to be delayed.

P12 you feel more at ease when the doctor has given you the treatment plan.

Participants identify that when a treatment plan is identified pre-treatment worry is reduced.

Participants do identify that early genetic testing may not be appropriate for all patients:

P3 you would have to be able to … 99% guarantee that it would be back within 3 weeks … the consultant would have to agree that 3 weeks wasn't too long to wait for surgery.

Nevertheless participants propose that clear information detailing the time required for genetic analysis is provided to assist patients in their decision to undertake the test:

P11 I would rather you told me then I know what I am dealing with (3 week wait).

P5 an explanation of why things are done … the time scales …explaining it properly from the outset.

Importantly this information will help patients if they proceed and while they wait for results.

Best time?

Participant responses are categorised into 3 broad groups: 'it makes sense', 'part of the package' and 'tailored treatment'.

It makes sense

Despite genetic testing representing an extra activity and psychological burden participants regard early testing as an intelligent choice:

P2 I know it's a lot to go through but it would make sense to have it all done … it would be good to have genetics there at diagnosis.

P10 that makes sense, it is more sensible to do it at that time … it makes sense to do it right at the start.

Additional confirmation is seen when participants compare their post-treatment testing experience with the proposal for early genetic testing:

P10 at the very start … better time to do it … it would be better … get it over & done with, deal with it at that time.

A commonly held opinion views the patient as an active participant in the treatment decision:

R15 offering the test & giving information is much more proactive, so many people would like to get it right in their own brains to actually deal with it.

Coping style is understood from participant dialogue to influence whether the test is proposed by the patient or healthcare professional. However within the study population coping style is not considered to impact uptake of the test. Participants view the test as enabling an informed decision; furthermore, they recognise that this is beneficial.

Part of the package

Overwhelmingly participants identify that early genetic testing should occur close to diagnosis:

> *P3 blood should be taken the minute you are diagnosed … the big thing to put across … (it is) for their treatment.*

It is acknowledged that there is no ideal time. However participants favour allowing the patient the option to decide:

> *R11 giving people the option, the choice … there's not really a good time (laughs)*
>
> *P2 brought up at the diagnosis talk through but leave it up to them as to when and if they have it.*

When the BRCA1/2 test proposal is not achieved at or very close to diagnosis alternative times are proposed by participants. These fit broadly into two categories: before surgery and after the cancer treatment.

The option to carry out testing before surgery presents a variable timescale. When surgery is scheduled before chemotherapy:

> *R2 after the first week (after diagnosis) but before you got your surgery.*

Similarly when neo-adjuvant chemotherapy is planned:

> *P1 before then (chemo), get a test before all the chemo is in your body.*

Within these dialogue participants identify that the patient may want time to come to terms with their cancer diagnosis or that fitting in the genetic consultation may not be feasible when the focus is pre-treatment procedures.

> *P3 fit the genetics into there that is probably the place to do it … even with chemo there is still about a month between diagnosis & starting chemotherapy.*

Recurrent focus is placed on the urgency to obtain genetic information on which to base primary treatment decisions.

When early genetic testing integral with diagnostic and treatment planning procedures participants anticipate, based on personal experience that the impact will be less that when testing is undertaken post-treatment:

> *P10 I probably would have been more ready for it at that time because you would get everything else done as well …part of your package of what you are doing … better because you are carried along … it is a busy time, you are getting all these things done and I think it would be more acceptable, probably would have been for me…it should be during the process of going through all your surgicals (pre-operative tests), your chemos (pre-chemotherapy rather than after… get it over with (laugh), get it over & done with, deal with it at that time.*

When testing is included with diagnostic and planning procedures high patient acceptance is anticipated by participants:

> *R16 'get tested, get the results back, make decisions and treatment is a ton better'… this is the test, you've got it (BRCA), you've got breast tissue on both sides, it all needs to be got rid of.*

A recurring theme of identifying a clear, treatment pathway is commonly presented.

An alternative option that is presented is to carry out genetic testing after breast cancer treatment. Within the study population the dominant testing pathway is

undertaken after primary cancer treatment to inform prophylactic interventions. A recurring theme is to first deal with the 'lifesaving stuff':

> *P11* let's just get over with the lifesaving stuff now.
>
> *R2 the person doesn't have to get the result until later you could still tailor the (prophylactic) treatments.*

Participants identify the impact of a cancer diagnosis and treatments*:*

> *P5 get through this (diagnosis) and my treatment and then consider (genetic test).*
>
> *R15 you have enough to deal with.*

While it is anticipated that treatment and genetic test experiences of participants are significant factors, these opinions highlight that they support the offer of early genetic testing. Furthermore they indicate that patients will themselves decide whether to undertake testing immediately or delay until after primary cancer treatment. These participants recognise that genetic information obtained via either pathway increases treatment choice and patient outcomes.

Closely associated with the option to propose genetic testing is the consideration of 'too much information'. Participants describe an optimum mental state for the provision and receipt of genetic information:

> *P4 are you going to be in the right frame of mind at the time? (pause) would it affect your choices? would it be too much? would you take it in at the time of diagnosis?*

A feeling of emotional overload can occur at diagnosis:

> *P5 I don't necessarily think that everyone would take that in at that time… there is a lot of information … you are bombarded with and it's all things you don't know about … I don't just mean the genetics … suddenly thrown in … you walk in for a check-up and come out with this happening, you are like 'bang, bang, bang' (moving hands) 'it's this, this, this' … just getting your head round everything.*

However a commonly held alternative choice and opinion is to deal with genetic testing at the same time as diagnosis:

> *P10 you are in shock anyway so get it over with (laugh).*

A similar view presents genetic information as something you may not wish to know but that should be dealt with:

> *P7 it's kind of like when somebody is dying and they're needing (pause) kidneys or something and the approach (for organ donation) you've got this horrendous thing in one hand and you are getting hit with something else*

Presenting the BRCA1/2 test option and the benefit that genetic information can bring to treatment decisions is consistently suggested:

> *P5 it would probably be better that they knew … I don't regret having that at the outset, at diagnosis … it's a lot to take in and consider, all the treatments & everything (genetic) they are throwing at you.*

Participants propose that following the BRCA1/2 test option, even if it is initially considered an extra burden, patients will consider and discuss the test:

> *P6 it's a lot to take in at the time but when ye' (you) think … get home an' (and) then ye' think, it sinks in (slowly).*
>
> *P8 go away and perhaps discuss it with their family … or best female friends … leave it for a few weeks and think about it.*

To offer a second appointment for further genetic discussion is recurs:

> *P11 the door is not going to be shut, you can come back.*

Participants propose that personalised proposals for genetic testing will enable the patient to consider an early test or to delay the choice. Indicating that an individualised offer and discussion will enable patients to retain control and make active, informed treatment decisions.

Tailored treatment

Personalised care is a dominant theme when participants consider hypothetical situations and reasons for undertaking early testing:

> *R2 helping to protect me, treatment could be tailored towards whatever gene I had.*

Participants identify clear treatment options in response to established genetic risk:

> *P4 discussing it at diagnosis could potentially make people deal with things differently.*
>
> *R14 knowing what gene they had and what steps to take and what course of treatment would be more appropriate … the doctors could assess what kind of surgery was more appropriate for the different strains.*

Support is widespread and irrespective of participant's genetic test experience and BRCA1/2 status. However for participants who undertook testing close to diagnosis support is accentuated.

Additional consideration is given to the psychosocial factors associated with extensive surgery that is required when a BRCA1/2 mutation is identified:

> *P8 it must be a great help (reconstruction) that it gives them more courage to face the surgery … you don't have a choice, you know it's serious and it's got to be done, this can be done for you to help you look at yourself as you would normally think of yourself.*

Participants recognised that early testing to inform personalised treatment can promote the best care for the individual. Furthermore they identify that when immediate reconstruction is appropriate this can be carried out for cosmetic and psychosocial benefit.

The study population support early genetic testing for all newly diagnosed HBOC patients. Breast cancer diagnosis for the study population is commonly received at a young age, between the age of 37 and 50 years. This may account for their

overwhelming emphasis of younger patients, who are consistently identified, as gaining the greatest benefit from early genetic testing:

> *R16 particularly a younger person, it's a no brainer.*

Fear, relating to cancer-risk, may be a significant factor that motivates participants to promote early testing for the younger patient group. It is anticipated that this relates to maximising survival, reducing risk and treatment interventions. Further support is presented within participant opinion:

> P8 *especially younger women with young families late 30s & early 40s … it makes complete common sense … offering it to them and maybe then if there was a faulty gene avoiding all of this and all the stress it causes for everyone around you.*

Furthermore within the dialogue surrounding this extract the participant referred to her experience of 3 cancer diagnoses, the impact of these and the associated treatment, for herself and family. They propose that getting the right treatment early is a recurring reason for undertaking the test, particularly when the younger HBOC patient is considered.

Participants identify that within the newly diagnosed patient population, not all have knowledge of their HBOC:

> *P4 would that be offered somebody with first breast cancer in a family?*

They recognise that such patients may not consider genetics when their cancer is diagnosed:

> *P10 it is a different kind of thing … I didn't … but I think it is something that you really should know about.*

Where HBOC risk is clinically identified participants recognise the value of proposing early genetic testing.

Recommendations

Throughout these interviews the participants actively considered and disclosed suggestions, for improving the evolving genetics and breast care services. It is relevant to present the range of participant opinions to assist in the identification of plausible and acceptable approaches to improving the genetic test experience with a view to improving breast cancer management and patient outcomes. The proposals fit into two categories: 'Who should propose testing?' and 'It would be better if…'

Who should present genetic test option

Overwhelmingly participants advise that a member of the Clinical Genetics team makes the first proposal for early genetic testing:

> *P6 somebidy (somebody) from genetics they have more knowledge … if they (patient) had any questions, then they'd be able t' (to) answer them.*

Increasing the presence of the genetics team within the FHBCC is recommended:

> *P10 would make sense to have strong presence … I haven't seen her in a long time, at a family history clinic … should be someone there especially for new (patients).*

The proposal may be more easily received when it is made by a healthcare professional with whom a relationship has been established. The suggestion to involve the MacMillan nurse:

> *R2 continuity of a Macmillan nurse, the same Macmillan nurse made a big difference, she could appear at different places to support me at a visit protected you, stuck up for you, she could be there for genetic testing.*

Alternatively, the surgeon and genetics nurse or doctor could make the first proposal:

> *P4 a joint clinic (surgeon and genetic) you don't want to ask a question for them to go 'well we are not sure, we'll let you know'.*

When considering these responses a multi-disciplinary team approach may be the most appropriate. Participants identify that if questions cannot be answered during the early genetic test discussion, the decision to undertake early testing may be delayed until the patient is provided with sufficient information. Of fundamental importance, members of this team should have the ability to answer genetic questions to ensure that the decision to undertake testing does not delay primary cancer treatment.

It would be better if…

- Preparing patients for genetic involvement can ease the process of establishing family history:

  R14 prepare people before they came up ... what questions …you need dates and times and what kind of cancers, I didn't have that information.

This proposal indicates that the patient experience could be improved by the provision of additional genetic information.

- Participants living the furthest distance from the main hospital expressed concern about impact of extra genetic appointments and their impact:

  P1 fair enough if you are in P or D (cities) but if you are 30+ miles from the hospital) and you are travelling ... kill two birds with one stone

  P6 I stay (15 miles from hospital) an' (and) if ye (you) had t' (to) go back t' (to) another (another) meetin' (meeting) ye (you) have t' (to) ask t' (to) get time off yer (your) work … I would prefer it together

This recurring suggestion to combine hospital appointments could minimise impact and promote uptake of genetic consultations for patient treatment and outcome benefit.

- Increase psychological support provision throughout the testing process:

    R2 overall, the whole situation, the medical side was very good but felt that very often the psychological side was lacking.

Recurring throughout the data participants recommend that support for patients could improve the genetic test and treatment choice experience.

- Where resources are limited:

    P3 if you can only do so many in the 3 week bracket that's the people who should be targeted (greatest benefit).

    P8 almost would save money throughout the NHS.

Participants identify that NHS resources are limited and that intelligent allocation of services is required.

9. DISCUSSION

Research is required to fully realise the benefits and impacts of Personalised Medicine. This small study is relevant to two recent proposals for evidence based research. The recent NICE guideline for familial breast cancer recommends that research is undertaken to identify the benefits and risks of early genetic testing (NICE, 2013b). It proposes patient experience, as one of 4 research areas, in which evidence is required to establish service delivery. Similarly an international gap analysis identified a research agenda that includes individuals with a genetic predisposition for breast cancer (Eccles et al., 2013).

The aim of this study has been to investigate experiences and opinions of genetic testing for the highly penetrant BRCA1/2 genes and the impact these have on treatment decisions. This investigation has been conducted in a single NHS Clinical Genetics setting, with in-depth interviews occurring in during 2012 and 2013. Targeted sampling used a convenience group of women, who undertook BRCA1/2 gene testing between the late 1990s and 2012, testing occurred close to the time of diagnosis or following primary breast cancer treatment.

Study data has been analysed utilising qualitative methodology to compare and illustrate genetic test experiences, opinions and treatment decisions. The study population is small, correspondingly the findings are not intended to be representative of a wider HBOC population. Understanding has been derived from narratives and interpretation of the data, not from published theory. However, where theory exist these have been applied to test the themes, only after they had evolved from the data. While early and interim literature reviews revealed no early genetic

test theory, the review was conducted following analysis and thematic development revealed new early genetic test theory. This was used to corroborate study findings, and assist deductive theory development.

The researcher has adopted a neutral and reflexive stance throughout the study. While the study has a genetic counselling focus, the researcher is not a genetic counsellor. This may be viewed as a limitation however neutrality permitted candid dialogue and investigation of the patient experience.

The discussion that follows presents the study findings according to the objectives and using associated headings. Factors that influence patient decisions and plausible clinical approaches are woven throughout the text.

The Genetic Test Experience: Why, Who, When & How?

The dominant reason for, women in this study, undertaking early genetic testing is to maximise survival. Conflicting earlier, and possibly out-dated, interpretation (Julian-Reynier et al., 1998) identifies that women with a cancer diagnosis attend genetics clinics, to learn why they have cancer and to inform family members of their risks. In contrast, Julian-Reynier (1998) reports that predictive testing is undertaken to establish cancer-risk. Therefore if viewed from a current perspective, where early genetic testing is available, Julian-Reynier's (1998) predictive test group, and not those with a cancer diagnosis, share characteristics with participants in this study who undertake early BRCA1/2 gene testing.

Participants indicate that maximum survival requires personalised cancer-risk knowledge, bespoke treatment and risk-reduction interventions based on genetic status. Correspondingly, maximising survival is reported by recent publications that identify this as a fundamental factor that motivates women, with hereditary breast cancer, to obtain BRCA1/2 genetic information (Wevers et al., 2014, Jeffers et al., 2014). In this study, the survival theme not only relates to extending life but to ensuring that quality of life is preserved. Similarly findings that support these results, are presented within a report that details 15 reasons for receiving rapid genetic counselling and testing (Wevers et al., 2012b).

Closely associated with the need to maximise survival, is family protection, although self-responsibility is identified, in this study, as the central factor that influences uptake of BRCA1/2 testing. Comparably, when considering genetic responsibility, self is reported as the first of 3 aspects (Etchegary et al., 2009). In corroboration with the Etchegary finding that identifies self-responsibility as a fundamental factor, participants in this study, convey that maximising survival and family protection are predominantly achieved by considering additional treatment options. Furthermore undertaking the most appropriate treatment, even when extensive, is viewed by these women, as offering the greatest self-protection, and lowest personal and family impact. In support of this opinion, a recent publication identifies that extensive surgery, including risk-reducing procedures, significantly improves 20-year mortality for women with a BRCA1/2 mutation (Metcalfe et al., 2014). Additionally participants in this study indicate that a younger patient group, may gain the greatest benefit from early testing. While this finding may be based on their personal experience; breast cancer diagnosis, for this study population, commonly occurred between 37 and 50

years of age. Similarly an Australian study identifies that women under the age of 50 want to be informed about treatment focused genetic testing (Meiser et al., 2012a) and relevantly, the risk of a hereditary breast cancer diagnosis is highest before the age of 50 (CGHFBG, 2001, Claus et al., 1996).

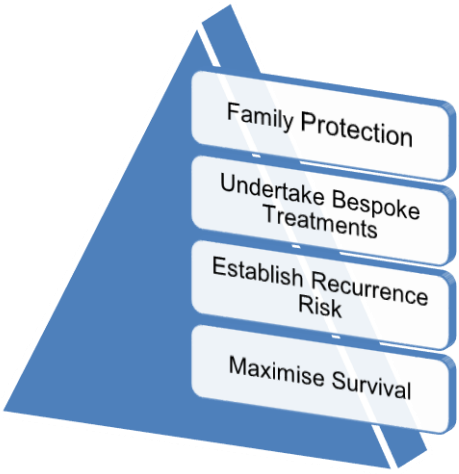
Participants convey the importance of reducing cancer-risk and minimising the need for subsequent surgery or treatments. Similarly, supporting this finding, researchers from The Netherlands have identified this phenomenon (Wevers et al., 2012b, Wevers et al., 2014). Furthermore additional family protection is anticipated, by participants, when genetic results can be shared with relatives. Genetic status information to inform and protect relatives, though a factor that influences the uptake and acceptance of BRCA1/2 testing, is acknowledged by participants as being lower priority when compared with advising treatment and risk-reducing decisions. Comparably, Etchegary (2009) reports that genetic information for others is the lowest priority genetic responsibility.

A hierarchy of needs that relate to the genetic test experience, summarising those reported by participants in this study, are presented in Figure 16: Hierarchy of Needs.

Throughout this study, coping styles have been identified, as influencing whether an individual seeks genetic information. Furthermore participants are identified as commonly alternating between styles, at different times in their cancer journey. Supporting this finding the GRACE tool (Phelps et al., 2010) indicates a range of

coping styles and mechanisms that can be anticipated throughout the genetic test process.

Figure 16: Hierarchy of Needs



In this study, it is understood that when participants adopt an information seeking style they commonly request genetic testing. They indicate information seeking behaviours to confront their fear of cancer recurrence, and to maximise survival. Conversely, within the study population, when individuals assume an avoiding style, they are less active in seeking personal genetic information, although they indicate ready acceptance of an offer for testing. However the offer, for these participants, is commonly made after primary breast cancer treatment. An established cancer-care model proposes patient information should take account of coping style (Miller, 1995). Supporting the finding that coping style influences access to genetic testing, early genetic testing protocols and care pathways should be developed to ensure equality of access, regardless of coping style (Vig and Wang, 2012).

Within the study population, participants who have an established family history attend the FHBCC. Correspondingly relationships with the multi-disciplinary team are established and HBOC information is shared; importantly acceptance of the BRCA1/2 test is high. Support and information provided by the Breast MDT are recognised, by participants, as aiding the genetic test process. While similar functions, structures and relationships are anticipated within UK FHBCCs. A remarkable finding worth mention is the frequency with which a particular FHBCC doctor is identified within dialogue relating to BRCA testing. This finding indicates that an interested and informed clinician can play a significant role in influencing test and treatment decisions.

Similarly, family cancer experience and cancer knowledge are identified as influencing the uptake of genetic testing. Participants with a significant family history report the greatest urgency for obtaining personal genetic information; it is *'a no brainer'*. Conversely, where family history is not established participants recognise that additional counselling and support may be required, to assist understanding of the relevance and uptake of early genetic testing. A study carried out in the Netherlands indicates that rapid testing should start within 5 days of a hereditary breast cancer diagnosis and provide results within 3 weeks (Wevers et al., 2014). Comparably, a proportion of the Dutch participants at diagnosis had an unestablished family history. Only one-third of their participants received results that contributed to primary cancer treatment decisions, however they report that rapid testing requires a complex clinical pathway.

The identification of a previously unknown or unrealised family history should be anticipated for a proportion of newly diagnosed breast cancer patients. In this study the experience of women with a young diagnosis, high risk tumour characteristics and an unestablished family history, differs from those with a known history who attend FHBCC. For patients who had previously not realised a significant family history, genetic counselling and the offer of an early genetic test will require more careful discussion and consideration to assist uptake of testing to inform treatment decisions. However, based on patient experiences revealed in this study, it is identified that coping style has a significant impact on timing of the genetic test and treatment choice. Participants identify that the development of clinical care pathways should ensure that when a high-risk hereditary breast cancer is diagnosed testing can be accessed rapidly; access should not be impacted by a previously unestablished history. Future research should explore treatment decisions and the genetic test experience for younger women with high risk tumour characteristics and a previously unestablished family history[67]. Furthermore a process for expediting family history information (where it is previously unestablished) should be established, to assist the early genetic testing pathway.

Participants in this study, indicate that patients should be appraised of the purpose of early testing; that the result can inform and optimise their treatment. Methods to improve the delivery and receipt, of early genetic testing patient information, have been proposed by participants in this study. Overwhelmingly, these women identify that the proposal for BRCA1/2 testing and results are best received during a

[67] Dialogue from participants (P3 & P12) indicate triple negative tumour characteristics. Tumour pathology data have not been collected (from medical notes) to verify the status; such activity is out-with the scope of this study.

personalised face-to-face discussion with a clinical genetics health care professional. They state that this will facilitate the most beneficial dialogue; crucially questions can be answered and significantly, when considering early testing, time is not wasted waiting for answers. This finding is in contrast with that of an Australian study; no clear preference was identified for which healthcare professional should first discuss early testing (Meiser et al., 2012b). Notably the clinical geneticist role is not presented within the Australian study; this may indicate an alternative healthcare structure. The clinical genetics role may be less well integrated than in the UK or that the role may be assumed by an existing team member. To enhance the discussion that proposes testing, participants identify that supplementary written information can aid the decision to undertake early genetic testing. Furthermore the Meiser (2012) study identifies patient preferences for information delivery, they emphasise the value of brief written information. Additionally results are awaited from a study that is currently being conducted to investigate how best to discuss early genetic testing (Watts et al., 2012).

Participants identify that NHS resources are limited and have proposed a range of practical, and relatively low cost, solutions to assist the integration of early genetic testing within the current FHBCC structure. Further research is indicated to identify methods for integrating genetic information and personalised medicine techniques with current clinical care. Correspondingly information delivery methods that assist early genetic test decision-making should be investigated. Furthermore, tools and clinical pathways to assist the delivery of early genetic test information should be developed.

A recent publication concludes that treatment focused genetic testing will in the future be integrated with oncology (Burcher et al., 2013). A finding of this study confirms the Burcher conclusion and identifies that the proposal to offer early genetic testing close to diagnosis, can be more readily attained when the Breast Care MDT is expanded to formally include the role of Clinical Genetics. Participants identify that *'it would make sense to have a strong presence at a family history clinic'*. Increasing presence of Geneticists and MacMillan Genetics Counsellors within the FHBCC would ensure that the genetic element of HBOC is a focus for the healthcare team and patients. This expanded MDT approach could facilitate participants' proposals for combined clinics which streamline care and resources for healthcare and reducing hospital visits for patients. It is proposed that when patients are newly referred to the FHBCC a consultation with a member of the Clinical Genetics team will identify those with the highest risk[68] and increase patient knowledge. Additionally participants recommend that genetics are present at diagnosis to *'back you up'* to ensure personalised treatment. Should an increased presence be adopted the integration of early genetic testing with diagnosis and cancer management can be achieved more readily.

A significant element of the test experience is waiting for BRCA1/2 results. Participant experiences demonstrate an acceptance of waiting for results, particularly when at the outset the purpose for testing and a clear time scale are presented. The waiting time is accepted by participants for *'that's the way it is'*. In support of early testing, participants describe that this time, between diagnosis and treatment, is when women start to accept their diagnosis and are typically busy with treatment

[68] Predictive testing may be indicated for those at greatest risk.

planning procedures. However when considering a 3 week wait for early test results urgency is identified, as a theme. In order to inform treatment, study participants state that rapid results must be available within the 3 week period. Furthermore where this is not possible it is proposed, by these women, that early genetic testing is not offered; primary cancer treatment should not be delayed by the test. Still, participants state that the benefit of '*tailored treatment*' outweighs any inconvenience associated with undertaking early genetic testing. Similar findings are reported by international research teams (Wevers et al., 2012b, Schlich-Bakker et al., 2007, Watts et al., 2012). Overwhelmingly a *'don't worry'* attitude is proposed when they wait for results. This and similar distraction coping strategies are indicated as appropriate in the GRACE tool, which can be adopted by the MDT to support genetic testing (Phelps et al., 2010).

It is identified that participants in this study, choosing not to involve extended family in their decision to undertake genetic testing, are afforded self-protection. Their testing decision is not challenged or influenced by external views. Additionally family protection is identified as a factor that may guide their decision, to withhold information until a definitive result is available, participants indicate that they aim to prevent worry. Alternatively this choice may be guided by fear, that external opinions may alter the decision for BRCA1/2 testing. Furthermore where relatives are involved, participants in this study reveal, that the individual undertaking testing may expose themselves to additional psychosocial stresses. Correspondingly this can impact (previously) supportive relationships. This finding conflicts with an earlier study that indicates support is gained when disclosing genetic information (Graceffa

et al., 2009). However the Graceffa study does not provide theory that relates to support and the decision to undertake testing or during pre-result period.

In this investigation, distress and loneliness have not been reported as responses to the genetic test. Such psychosocial responses can be anticipated and are described in publications that relate to breast cancer genetic testing (Wevers et al., 2011a, Valverde, 2006) although these reactions are not universally reported (Schlich-Bakker et al., 2007). However short-term anger has been described by participants in this study, although this is reported as a more exceptional reaction to the genetic testing experience. Anger, within participant dialogue, is identified as a response to a potential cancer-risk. In support of this finding, anger is reported as a valid emotional reaction when genetic inheritance is considered (McDaniel, 2005). Nevertheless studies that report highest levels of genetic distress relate to predictive testing (Kenen et al., 2006). Genetic testing carried out in response to a cancer diagnosis may diminish distress responses. Reinforcing this proposal, participants report that their focus is dealing with the cancer, maximising survival, and that the test while providing important information has a lower priority.

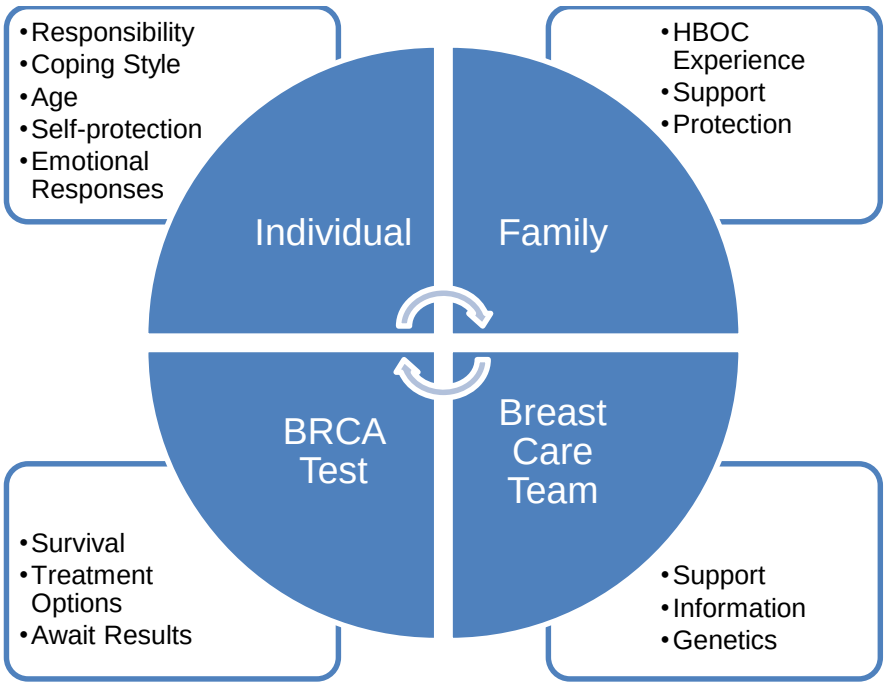
Participants identify that early genetic testing may not be appropriate for all newly diagnosed HBOC patients; where early genetic testing represents an added psychological burden testing they propose deferring testing until after primary cancer treatment. A comparable conclusion is found within a large randomised trial publication (Wevers et al., 2012a). Increased psychological support at diagnosis and during the genetic testing process have been identified, by participants in this study, as potential areas for clinical improvements. To maximise patient acceptance

specific focus is proposed around the areas of cancer-specific distress and the early genetic test.

It should be assumed that increased patient benefit is of principal importance. However enhancing professional awareness and knowledge of clinical genetics techniques, and their application, within the realm of Personalised Medicine is an added benefit that can be attained with integration. Genetic knowledge should be acquired by the extended breast care team, to facilitate genetic discussion that presents a uniform message and patient support. Furthermore managing expectations, by fully informing patients of the test process and sensitivity may assist to reduce potential anxiety relating to the wait and the result. Subsequent to this study, research should be proposed to investigate the experience and opinions of relevant health care professionals prior to fully adopting this progression.

Figure 17 summarises the inter-related factors that impact the genetic testing experience for these study participants.

Figure 17: Factors Impacting the BRCA Test Experience



Widespread support, for early genetic testing to inform treatment decision making, is demonstrated by participants. However the greatest endorsement is conveyed by younger participants and those who undertook early testing to inform their primary cancer treatment.

BRCA1/2 Results & Treatment Decisions

Participants in this study, have been recruited from a NHS Clinical Genetics Clinic convenience sample. While the study population is small, theoretical and purposive sampling techniques have been utilised with the aim of achieving proportional representation of patients with a BRCA mutation. Correspondingly, a BRCA mutation is identified in 30% (5/17) and no BRCA or a variant of uncertain significance in 70% (12/17) of the participants. Similar proportions can be expected within the HBOC population (Antoniou et al., 2003).

The BRCA1/2 result, in this study, is identified as the most significant factor influencing the treatment decision, informing women whether *'the big surgery'* is needed. Where results identify a BRCA1/2 mutation the dominant response, from this population of HBOC patients, is *'no surprise'.* Correspondingly women overwhelmingly choose to '*get in and get it done'*; they urgently undertake extensive surgery predominantly bilateral mastectomy, to maximise survival. While this intervention is not universally accepted by clinicians there is an increasing trend for this decision; an increased uptake of bilateral mastectomy at first surgery is reported in response to a BRCA1/2 mutation identified close to breast cancer diagnosis (Wevers et al., 2012b, Wevers et al., 2014, Metcalfe et al., 2014). Furthermore, participants in this study support early breast reconstruction surgery to *'put you back together'*, they identify that it offers cosmetic and psychosocial benefits that assist coping with a significant health decision. Recent publications also support a trend for immediate reconstruction within a BRCA1/2 patient population (Heemskerk-Gerritsen et al., 2014).

Coping style is identified as a significant factor that contributes to the individual's role in treatment decision making. Within the study population those who adopt an information seeking style at the time of treatment decision-making are more passive and depict acceptance of treatment proposals. Conversely participants who, at this time, adopt an avoiding style reveal greater involvement with the decision and treatment planning. While coping style is understood to influence the decision process, for participants with a BRCA1/2 mutation, it does not impact the decision.

Participant responses to BRCA1/2 gene analysis that revealed no mutation or a mutation of uncertain significance are however less consistent. Where a result does not identify a high risk BRCA1/2 mutation the dominant response, a '*false sense of security*'. Worry about a false negative result is associated with less predictable treatment decisions and treatment decision conflict. This reaction is not unwarranted, as women are informed that current genetic testing only identifies a BRCA1/2 mutation in approximately one quarter of HBOC patients. Similarly non-BRCA HBOC is also associated with increased cancer-risk, indicating that lifestyle factors and undiscovered genes may be responsible for the majority of HBOC.

Typically treatment decisions, for women with no BRCA1/2 mutation, are based on tumour characteristics (NICE, 2013a, Smith and Isaacs, 2011) although in this study, it is identified that age, family cancer experience and psychosocial responses to the cancer diagnosis impact treatment decisions. Furthermore, when no mutation or a BRCA1/2 mutation of uncertain significance is identified, coping style is the fundamental factor influencing treatment decisions. Participants who assumed an avoiding coping style, report being guided by the test result and medical advice. Most commonly, these women undertook breast conserving surgery, however treatment decision conflict is commonly reported, in association with disbelief and worry about a false result. Conversely when an information seeking coping style is adopted participants portray being more active in the treatment decision commonly undertaking the most extensive procedure, bilateral mastectomy (often with reconstruction). In such circumstances, the participant declares result disbelief and correspondingly they assume increased cancer-risk, subsequently this fundamental factor motivates the treatment choice. A recent publication concludes that where no

mutation is identified, genetic status should guide treatment (Rhiem et al., 2012) and indicates that breast conserving surgery is most appropriate and not the extensive interventions commonly undertaken by those with an information seeking coping style. However publications indicate a broad variation in surgical treatment choice and propose that additional research is required to guide treatment decisions for these patients (Culver et al., 2013, Murray et al., 2011, Huzarski et al., 2013). During the course of this study, the question of establishing the psychosocial impact of early genetic testing has recurred; most concerning is the '*false sense of security*' or disbelief that participants report in response to a BRCA1/2 test that does not identify a high-risk mutation. A comprehensive investigation of the patient response to a negative test is proposed to increase understanding and develop an appropriate clinical care approach for post-test genetic and treatment decision counselling. Furthermore it is proposed patient information delivery and treatment decision tools are developed to minimise result disbelief. In addition follow-up counselling may be indicated to determine whether treatment decision conflict occurs, and correspondingly address such a response.

When considering the treatment plan participants in this study recommend that '*the bigger surgery*' is '*pencilled-in*' while BRCA1/2 test results are awaited. They advise this to ensure that, should a BRCA1/2 mutation be identified, resources are in-place and the '*tailored plan*' is not delayed. Comparably, the Australian research team report logistical challenges when scheduling, and rescheduling, interventions (Wevers et al., 2014). Evolving Personalised Medicine brings with it impacts for current clinical care systems that should not be underestimated, they require flexible patient management systems and progressive health care roles (McGowan et al.,

2014, Joly et al., 2014). Additionally when considering patient management or service planning challenges it should be recognised that the HBOC population is approximately 5-10% of the total breast cancer population and only 20-25% are anticipated to carry a fault in a BRCA1/2 gene; within a local health care population patient numbers are small.

BRCA status, age, tumour characteristics and family history are identified as factors that influence the uptake of risk-reducing interventions. In-keeping with the survival theme, more urgent action is required and taken, by participants, when a BRCA1/2 mutation is identified. Similar to primary cancer treatment decisions, when no mutation is identified choices are less predictable and coping style is a fundamental factor. Women identified as adopting an avoiding coping style express that they gain reassurance, correspondingly they do not require or undertake additional prophylactic procedures. Conversely, participants who assume an information seeking style indicate that they are more likely to undertake risk-reducing prophylactic interventions.

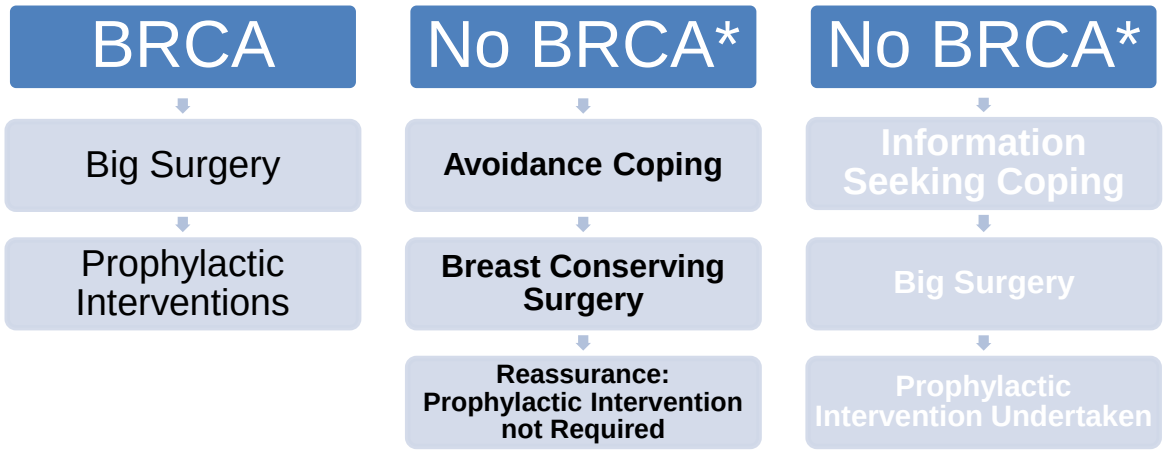
Within the study population the response to the BRCA test is commonly amplified by factors such as age, prior cancer experience, support, knowledge and coping style; each of these factors can impact treatment decisions. Participants identify that treatment decision-making should be supported and guided by the clinical team. However an important role of the Genetics Counsellor is to provide support and information that assist the patient, while taking account of coping style, to assimilate BRCA1/2 test results and their impact. Current roles and knowledge should be fully explored prior to implementing appropriate clinical education, with expansion and

definition of roles that support treatment decisions informed by early BRCA1/2 test results.

An overview of treatment decisions and coping styles identified in this study are provided in Figure 18.

For participants with results that identify no high risk BRCA1/2 mutation, including those with a BRCA1/2 variant of uncertain significance, it is of particular relevance that genetic blood samples are retained for future testing. Overwhelmingly participants in this study accept that current scientific techniques are not able to identify all of the possible faults on the BRCA genes, they acknowledge that future scientific advances may improve testing sensitivity. Furthermore, women indicate hope and anticipate relief should a mutation be identified with (future) re-testing. Estimates report that BRCA1/2 mutations account for between 10-40% of familial breast cancer (Shuen and Foulkes, 2011), suggesting that additional undiscovered genes and lifestyle factors are responsible for a high number of hereditary breast cancers. Genetic and treatment counselling should take into account the role and impact of future re-testing. Caution will be required, to avoid creating disbelief or worry about a false result.

Figure 18: Treatment Decisions in Response to Test Results & Coping Style



Key * Tumour characteristics, age at diagnosis and family history / genetic risk prediction are also considered.

When considering additional prophylactic surgery, for the associated ovarian cancer risk participant treatment decisions are less predictable. A pilot study by a team from the Netherlands similarly found 46% of participants undertaking early genetic testing to obtain certainty for their ovarian cancer-risk (Wevers et al., 2012b).

Understanding, taken from narratives, indicates that this relates to the absence of suitable ovarian surveillance procedures. Within the study population, oophorectomy is commonly undertaken before genetic testing, and generally the decision is based on genetic risk prediction. However where surgery had previously not been considered, BRCA1/2 status informs this risk-reducing decision, although the younger women, in this study, describe child-bearing as adding further complexity to the prophylactic ovarian surgery decision. These findings are supported by a recent quality of life study that reports reduced cancer worry, in response to ovarian surgery when a BRCA1/2 mutation is identified (Finch et al., 2013).

Participants identify the impact of health behaviours on cancer-risk and prognosis although they question the impact of positive health behaviours at diagnosis and when test results are received. It is not known if this response is typical though a similar response is seen in publication (Valverde, 2006). Genetic results can be used to reinforce healthy behaviours (McBride et al., 2010) and risk-reduction strategies (Guinan et al., 2013a) to improve patient outcomes. Participants identify that they are uncertain about the benefits of positive health behaviours when faced with both HBOC and a BRCA1/2 mutation. Correspondingly clear guidance, identifying health behaviours that provide the greatest benefit should be incorporated into hereditary breast cancer risk-reduction counselling to further improve prognosis. Furthermore, while many personalised interventions are require either increased healthcare resource or budgets health behaviour interventions can be relatively low-cost. Research to identify the most important health behaviours is proposed.

Test Timing & Treatment Decisions

Within the NHS Tayside Clinical Genetics service early genetic testing remained uncommon during study recruitment. Following breast cancer diagnosis BRCA1/2 testing was undertaken, by study participants, between 1997 and February 2012; predominantly testing occurred after primary cancer treatment. Today cancer treatment for the majority of patients starts 3-4 weeks after diagnosis, although participants indicate a wider time range for the start of their treatment. Purposive sampling has been used throughout recruitment to ensure representation from patients who undertook BRCA1/2 genetic testing close to breast cancer diagnosis. A higher proportion of patients today could be expected to undertake early genetic testing; this expectation relates to current clinical guidelines (NICE, 2013b). National

clinical guidelines that provide clear early testing eligibility guidance should be anticipated.

Within the study population a fundamental factor influencing the genetic test experience is the length of time taken to obtain results. However it is predicted that in light of modern testing techniques (Wevers et al., 2012b) and the 3 week guideline, for early test results, the consistent long wait experienced by these participants is now out-dated. Today, the option to take a genetic blood sample close to diagnosis, and before or while pre-treatment tests are carried out, is not expected by clinicians to impact or delay primary cancer treatment. Furthermore, it is anticipated, in light of national clinical guidelines that early genetic testing will increasingly be proposed. Delivery of early BRCA1/2 testing from newly diagnosed hereditary breast cancer will requires an efficient process to ensure that results are available within the 3 week guideline; this carries significant resourcing implications. However resourcing should also consider the small group of patients with particularly aggressive tumour characteristics (arguably those with greatest need for early genetic testing) who require rapid neo-adjuvant chemotherapy; testing may be required more urgently to maximise DNA quality.

In attempt to rationalise the proportion of women undertaking testing after primary cancer treatment, participants report discussions with healthcare professionals that consider the *'lifesaving stuff'* more important than early testing. Personalised medicine is changing this culture. Healthcare professionals now have a greater knowledge and acceptance of the value of BRCA1/2 gene testing within a HBOC to inform treatment (Burcher et al., 2013). Correspondingly more women now have a

greater appreciation of the relevance and request personal genetic information (Meiser et al., 2012b).

BRCA1/2 testing, and the associated implications, is proposed by study participants as something that *'you don't want to hear'*. However participants identify that early testing is *'a no brainer'* and based on their experiences, they recommend that (you) *'get it over with'.* In this study, it is identified that, the test provides important additional information *'so that you can get on with it'*, the most appropriate treatment and if necessary risk-reducing interventions, and then *'get on with your life'*. Study participants describe that the result enables patients (and their care team) to identify *'tailored treatment'* to reduce cancer risk and avoid further interventions.
Similar results, supporting these findings, are found in a qualitative study investigating treatment focused genetic testing (Meiser et al., 2012b).

A cancer diagnosis is life-changing and around the time of diagnosis patients can feel overwhelmed (Meiser et al., 2012a). Participants concur, and identify that information, *'all things you don't know'*, is provided during the diagnosis consultation. However they state that significant health and life decisions are required. While participants recognise that there is *'not really a good time'* to raise the option for early BRCA1/2 testing to inform treatment they recognise that early genetic testing can assist these significant treatment and risk reducing decisions. Appropriate information and counselling for patients, who would benefit from early genetic testing, should be tailored to address such concerns. Correspondingly the Meiser (2012) study provides support for this finding.

Less commonly participants in this study chose to defer gene testing. Correspondingly participants identify that when testing is deferred subsequent *'tailored'* risk-reducing intervention, based on genetic risk, may be required. Probable explanations for deferring are that planned treatment (mastectomy) was based on predicted risk and family history was unestablished before diagnosis. Furthermore, relevance of testing is identified as the factors that pertain to the participants who deferred testing. An earlier study (Schlich-Bakker et al., 2007) that investigated the reasons for withdrawal from genetic testing reports a higher proportion (30%), than this study (12%), of women declining or withdrawing. Corresponding with the factors, identified in this study, as relating to test deferral the Schlich-Bakker (2007) publication reports that immediate decliners do not consider the test to be relevant. Maximising survival is the fundamental theme, in this study, that influences uptake and participant support for early genetic testing. Participant dialogue relates to responsibility for self and gaining certainty about cancer-risk, these themes are identified as foremost when patients choose to undertake early testing. Similarly maximising survival, is considered by participants, to be more significant than any foreseen psychosocial distress that may be anticipated in response to genetic testing. A recent literature review reports an overlap of cancer-specific and genetic psychosocial distresses when considering cancer genetic testing (Eijzenga et al., 2014). Results of a large randomised controlled trial investigating the psychosocial impact of early BRCA1/2 gene testing are currently awaited (Wevers et al., 2011a).

Significantly, when an early test is undertaken, participant treatment decisions include risk-reducing prophylactic interventions. Conversely a test taken after primary cancer treatment informs only risk-reduction. Hypothetical questions have

been used to explore early testing opinions where women undertook testing after primary cancer treatment, although it is understood that their responses are based on genetic test and breast cancer experiences. Regardless when their test was carried out these participants propose that early testing is *'part of the package'* and integrated with diagnostic and cancer management procedures. Correspondingly an Australian team identified that early testing should be incorporated with the routine clinical assessments (Meiser et al., 2012a). Furthermore women in this study identify that when early testing is an option it is *'better to know at the start'* to avoid the need to *'go back in'* for additional treatments. When participants who undertook testing after primary cancer treatment consider a hypothetical early test they indicate that *'not everyone will take it in'*. This is a less common opinion however associated with the view they describe that diagnosis may be overwhelming or that the relevance of early testing is not appreciated. Correspondingly, although infrequently, participants advise caution; the offer should include choice and the opportunity to defer testing when primary cancer treatment ends. A comparable proposal is found within an ongoing randomised controlled trial (Watts et al., 2012).

The findings from this study, demonstrate patient support for an early BRCA1/2 test proposal, to inform treatment decisions.

10. CONCLUSIONS

Early genetic testing can inform breast cancer treatment. This qualitative investigation provides new knowledge of the patient experience and acceptability.

Why offer early genetic testing?

BRCA1/2 mutations are by far the most common cause of hereditary breast cancer (Miki et al., 1994, Wooster et al., 1995). Within a hereditary breast cancer population women who present with breast cancer, and a significant family history, are most likely have a fault in the highly penetrant BRCA1/2 genes (Eccles and Pichert, 2005). BRCA-related tumours are typically more aggressive and respond less predictably than sporadic cancers (Shuen and Foulkes, 2011). Studies indicate that early knowledge of BRCA1/2 status brings significant benefit; treatment decisions can be tailored to incorporate genetic status and the most clinically appropriate interventions (Trainer et al., 2010a, Wevers et al., 2014). For those women with a BRCA1/2 mutation extensive interventions that include risk-reduction significantly improve prognosis (Metcalfe et al., 2014).

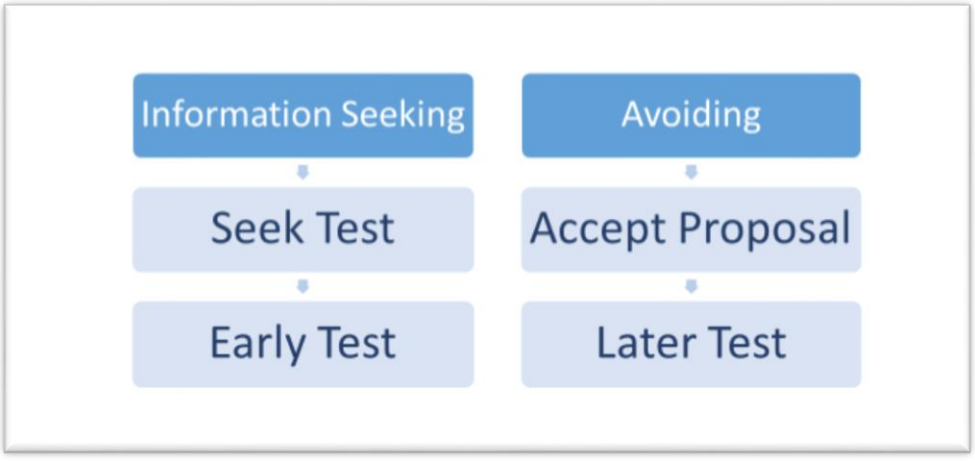
Why do women seek early breast cancer genetic information?

Women, participating in this small investigative study, indicate that maximising survival is fundamental when high-risk breast cancer is diagnosed. Correspondingly, this theme is associated with justifications for pursuing early BRCA1/2 testing. Significantly these women identify a responsibility for obtaining genetic information to afford self-protection. They recognise that genetic information, obtained close to diagnosis, can inform treatment and risk-reducing interventions. Furthermore,

participants identify that preserving length and quality of life affords family-protection. This factor motivates women to seek early genetic information, particularly when children are dependant. The provision of genetic information for the family is acknowledged as an incentive for undertaking early testing however maximising survival, their main concern, has the greatest significance.

In this study coping style, age, family cancer experience and cancer knowledge are identified as factors that influence why women seek genetic information (see Figure 19: Coping Style & Genetic Testing). Most significantly coping style is understood to affect whether women, in this study, request the test. While women are recognised as alternating between coping styles, throughout their cancer journey, an information seeking style is associated with those who request early genetic testing. Conversely, women identified as adopting an avoiding style are less likely to actively seek genetic information. However they reveal ready acceptance of a proposal for testing. Clinical practice should account for these differences and provide equality of access to early genetic testing.

Figure 19: Coping Style & Genetic Testing



While women commonly state that BRCA1/2 genetic information, and the associated cancer-risk implications, is not something they choose to seek they recognise that genetic information brings '*clarity*' to treatment decisions and the option for '*tailored treatment*' makes early testing '*a no brainer*'. Cancer diagnosis can be overwhelming. Nevertheless participants support obtaining genetic information close to breast cancer diagnosis and indicate that these benefits outweigh any perceived burden.

The patient experience: psychosocial burden?

The genetic test is predominantly undertaken, by women in this study, after primary breast cancer treatment. However in response to their experience participants favour early BRCA1/2 testing to inform treatment, for women with a high-risk hereditary breast cancer diagnosis. Additionally participants indicate accentuated benefit when diagnosis and early testing occur at a young age. Furthermore, it is anticipated that the recent NICE clinical guidelines will result in a higher number of women undertaking early genetic testing.

Commonly, for participants, family history is established before diagnosis, correspondingly increased breast surveillance and relationships with the breast care team are established. Participants indicate that '*growing-up*' with cancer increases knowledge and acceptance of genetic testing. In contrast, where high-risk tumour characteristics or diagnosis at a young age indicates genetic enquiry, coping style is identified as a significant factor in BRCA1/2 test patient acceptance and uptake. Correspondingly, for these women additional genetic counselling may be indicated.

Furthermore future research should explore treatment decisions and the genetic test experience for younger women with high risk tumour characteristics.

Concerns about the test adding unnecessary burden are not validated by this investigation, although participants identify that early testing is not always appropriate. Furthermore participants acknowledge that there is '*not really a good time*' to discuss BRCA1/2 testing. Uncommonly within the study population a test is deferred when early testing has an uncertain relevance for the patient. However, overwhelmingly participants recognise that early genetic results can substantially assist the significant health decisions that may be required close to diagnosis. Correspondingly at this time, women focus on maximising survival and subsequently, in this study, early genetic testing appears to be associated with lower levels of distress than predictive testing.

Participants recommend that early testing is undertaken within an integrated package of cancer diagnostic and intervention planning. An invitation for early genetic testing should state the benefit of '*tailored treatment*' and provide an option to defer testing, after primary cancer treatment has concluded. When testing is undertaken close to diagnosis, participants affirm that results are required urgently and should not delay primary cancer treatment. Furthermore, participants propose that extensive interventions are '*pencilled-in*' to ensure that resources are in-place and treatment is not delayed. Although when considering service planning challenges, small patient numbers can be anticipated, to require extensive interventions that are indicated when a BRCA1/2 mutation is identified. Further work is required to develop clinical roles and pathways that facilitate adaptable and

supportive treatment planning. Additionally it would be prudent to enhance professional education to gain maximum benefit from Clinical Genetic Personalised Medicine techniques.

Participants recommend that the early test proposal and genetic discussion will be most effective when delivered during a face-to-face consultation. In this study, the role of an interested and informed clinician has been identified as providing significant benefit to patients. Preference is indicated, by participants, for a Clinical Genetics specialist undertaking this role, although with training a member of the breast care multi-disciplinary team could adopt the role. Supplementary written information is proposed by these women, to reinforce the discussion and aid the decision to undertake early genetic testing. Research is indicated to develop tools that assist effective patient communication. Furthermore it would be prudent to explore healthcare opinion prior to expanding current clinical roles or further integrate Clinical Genetics within the Breast Care Multi-Disciplinary Team.

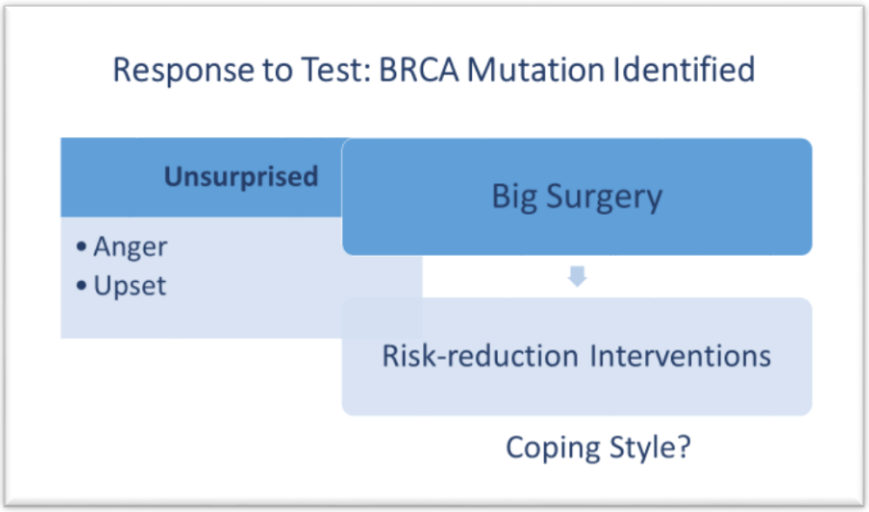
Does genetic information impact treatment decisions?

The result, and not timing of the test, has greatest impact on treatment decisions. Early establishment of BRCA1/2 status provides personalised cancer risk information that can inform treatment and risk-reduction decisions. Furthermore genetic information has the potential to reinforce positive health behaviours, improving cancer-risk and prognosis.

Within a hereditary breast cancer population when a BRCA mutation is identified participants report feeling unsurprised. When this knowledge is available prior to

primary cancer treatment, participants identify that extensive surgery and prophylactic interventions can combined at the initial procedure with the aim of increasing prognosis and avoiding further interventions (summarised in Figure 20). Furthermore, where appropriate, surgery can incorporate immediate breast reconstruction to '*put you back together*'. Participants regard extensive interventions as offering the greatest risk-reduction, while reducing the personal and family impact of cancer and interventions. In the presence of a BRCA1/2 mutation coping style is understood to influence the decision process, but not the decision.

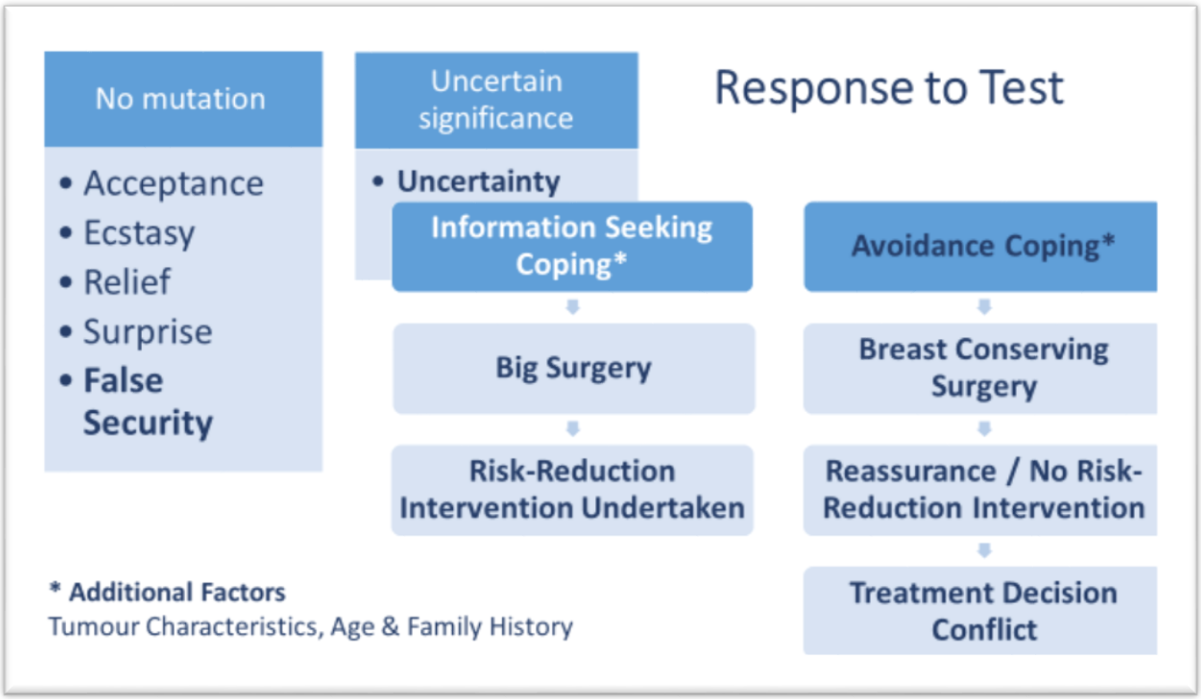
Figure 20: Response when a BRCA Mutation is Identified



Most commonly within the study population no high-risk BRCA1/2 mutation is identified; this finding is representative of a hereditary breast cancer population. Correspondingly, for the majority, less extensive, breast-conserving procedures would be clinically indicated. Reassurance may be anticipated although typically women in this study population report a '*false sense of security*' and disbelief. This response is associated with less predictable treatment and risk-reduction decisions. It is understood that, for these women, the coping style adopted at the time of treatment-decision making significantly influences choice. Furthermore where

disbelief endures treatment decision conflict can result (see Figure 21). The clinical and psychosocial implications of a '*false sense of security*', disbelief or worry about a false negative result should be fully investigated. This would assist the development of an appropriate clinical care approach for genetic and treatment-decision counselling.

Figure 21: Responses in the Absence of a High Risk Mutation

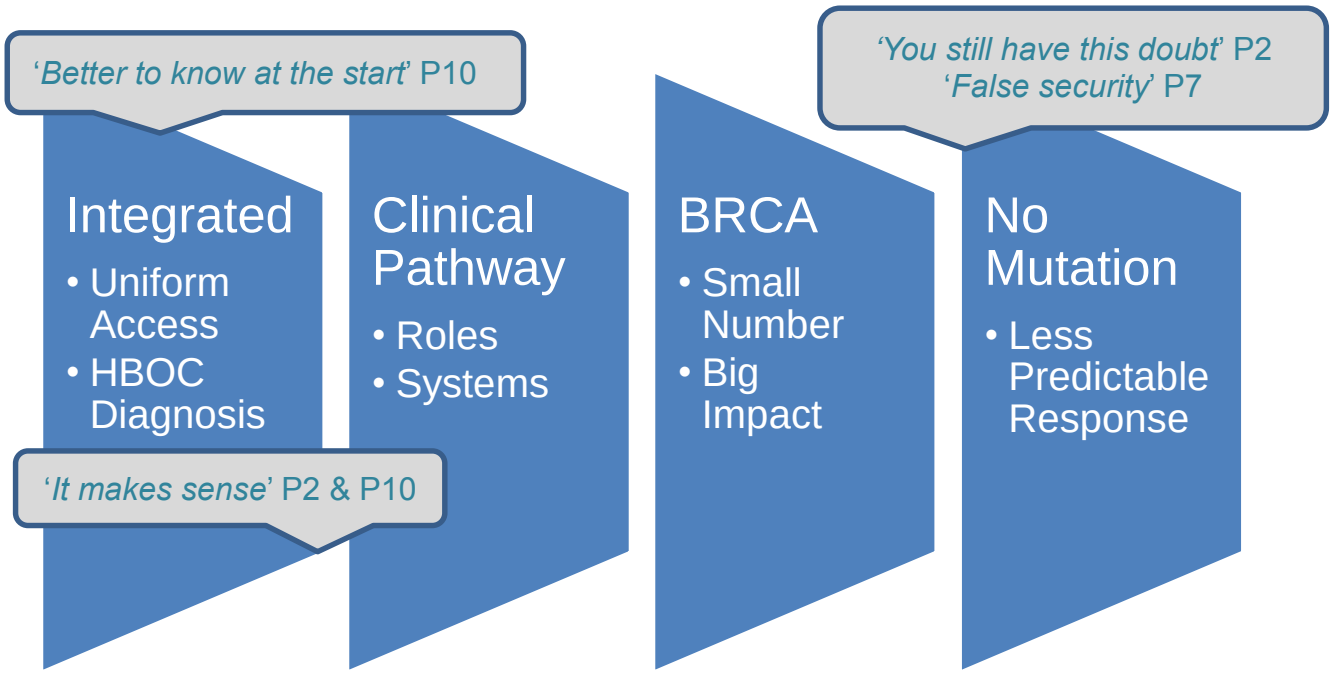


Clinical progression?

Women in this small study who have undertaken genetic testing following a hereditary breast cancer diagnosis endorse and support the use of early genetic testing to provide BRCA1/2 status information that can assist treatment and risk-reduction decision making. Participants overwhelmingly state that the benefit of early genetic testing and tailored treatment outweighs any inconvenience associated with the test and wait for results.

Regardless of when their test was carried out participants propose that *'it makes sense'* to integrate testing with diagnostic and cancer management procedures and propose that testing should be '*part of the package'*. Furthermore, the women in this study identify that it is *'better to know* BRCA status *at the start'* to avoid the need to *'go back'* for additional treatments (See Figure 22 for clinical recommendations).

Figure 22: Clinical Recommendations



Clinical integration should focus on developing early genetic testing protocols and that provides equality of access, regardless of coping style. Hereditary breast cancer clinical pathways should ensure early access when high-risk breast cancer is diagnosed. Furthermore, access should not be impacted by a previously unestablished family history. Future research should identify which roles within the extended breast care team are most appropriate for proposing and discussing the early genetic testing.

Adaptive cancer treatment planning systems will be required. While early genetic testing will be indicated for only 5-10% of the total breast cancer population no more than 25% of these women should be anticipated as having a test that identifies a BRCA mutation. Integrating adaptive systems will provide benefit to this small high risk group, who will subsequently benefit from personalised yet extensive interventions to maximise survival.

Clinical adoption of early genetic testing to inform treatment for newly diagnosed hereditary breast cancer appears to be acceptable and feasible. However the psychosocial implications of a '*false sense of security*' or worry about a false negative result should be fully investigated to assist the development of an appropriate clinical care approach for genetic and treatment-decision counselling.

REFERENCES

AARONSON, N. K., AMIR, E., FREEDMAN, O. C., SERUGA, B. & EVANS, D. G. 2010. Assessing Women at High Risk of Breast Cancer: A Review of Risk Assessment Models. *Journal of the National Cancer Institute,* 102**,** 680-691.

ABAD-PEROTÍN, R., ASÚNSOLO-DEL BARCO, Á. & SILVA-MATO, A. 2012. A survey of ethical and professional challenges experienced by Spanish health-care professionals that provide genetic counseling services. *Journal Of Genetic Counseling,* 21**,** 85-100.

ABCSG 2000. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br J Cancer,* 83**,** 1301-8.

ADJUVANT!, I. 2003-2011. *Adjuvant! Online* [Online]. Available: http://www.adjuvantonline.com/index.jsp.

ALBADA, A., VERNOOIJ, M., VAN OSCH, L., PIJPE, A., VAN DULMEN, S. & AUSEMS, M. G. 2014. Does and should breast cancer genetic counselling include lifestyle advice? *Fam Cancer,* 13**,** 35-44.

ANDRYKOWSKI, M., LIGHTNER, R., STUDTS, J. & MUNN, R. 1997. Hereditary cancer risk notification and testing: how interested is the general population? *Journal of Clinical Oncology,* 15**,** 2139-2148.

ANTONIOU, A., PHAROAH, P. D. P., NAROD, S., RISCH, H. A., EYFJORD, J. E., HOPPER, J. L., LOMAN, N., OLSSON, H., JOHANNSSON, O., BORG, Å., PASINI, B., RADICE, P., MANOUKIAN, S., ECCLES, D. M., TANG, N., OLAH, E., ANTON-CULVER, H., WARNER, E., LUBINSKI, J., GRONWALD, J., GORSKI, B., TULINIUS, H., THORLACIUS, S., EEROLA, H., NEVANLINNA, H., SYRJÄKOSKI, K., KALLIONIEMI, O. P., THOMPSON, D., EVANS, C., PETO, J., LALLOO, F., EVANS, D. G. & EASTON, D. F. 2003. Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *The American Journal of Human Genetics,* 72**,** 1117-1130.

ANTONIOU, A. C. & EASTON, D. F. 2006. Models of genetic susceptibility to breast cancer. *Oncogene,* 25**,** 5898-5905.

ANTONIOU, A. C., PHAROAH, P. D. P., MCMULLAN, G., DAY, N. E., STRATTON, M. R., PETO, J., PONDER, B. J. & EASTON, D. F. 2002. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *British Journal of Cancer,* 86**,** 76-83.

ARDERN-JONES, A., KENEN, R. & EELES, R. 2005. Too much, too soon? Patients and health professionals' views concerning the impact of genetic testing at the time of breast cancer diagnosis in women under the age of 40. *European Journal of Cancer Care,* 14**,** 272-281.

ARNEY, K. 2014. *Coming ever closer – first PARP inhibitor on track to be licensed in Europe* [Online]. London: Cancer Research UK. Available: http://scienceblog.cancerresearchuk.org/2014/10/24/coming-ever-closer-first-parp-inhibitor-on-track-to-be-licensed-in-europe/ [Accessed 30/03/2015 2015].

AUDRAIN, J., SCHWARTZ, M. D., LERMAN, C., HUGHES, C., PESHKIN, B. N. & BIESECKER, B. 1997. Psychological distress in women seeking genetic counseling for breast-ovarian cancer risk: the contributions of personality and appraisal. *Annals of behavioral medicine,* 19**,** 370-377.

BAO, W., HU, F. B., RONG, S., RONG, Y., BOWERS, K., SCHISTERMAN, E. F., LIU, L. & ZHANG, C. 2013. Predicting Risk of Type 2 Diabetes Mellitus with Genetic Risk Models on the Basis of Established Genome-wide Association Markers: A Systematic Review. *American Journal of Epidemiology,* 178**,** 1197-1207.

BARON, J. A. & HAILE, R. W. 1998. Protective Effect of Cigarette Smoking on Breast Cancer Risk in Women With BRCA1 or BRCA2 Mutations??? *Journal of the National Cancer Institute,* 90**,** 726-727.

BARTELINK, H., HORIOT, J. C., POORTMANS, P. M., STRUIKMANS, H., VAN DEN BOGAERT, W., FOURQUET, A., JAGER, J. J., HOOGENRAAD, W. J., OEI, S. B., WARLAM-RODENHUIS, C. C., PIERART, M. & COLLETTE, L. 2007. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *Journal of Clinical Oncology,* 25**,** 3259-65.

BARTLE-HARING, S., TOVIESSI, P. & KATAFIASZ, H. 2008. Predicting the use of Individualized Risk Assessment for Breast Cancer. *Women's health issues : official publication of the Jacobs Institute of Women's Health,* 18**,** 100-109.

BEERY, T. A. & WILLIAMS, J. K. 2007. Risk reduction and health promotion behaviors following genetic testing for adult-onset disorders. *Genet Test,* 11**,** 111-23.

BEGG, C. B., HAILE, R. W., BORG, Å. & ET AL. 2008. Variation of breast cancer risk among brca1/2 carriers. *JAMA,* 299**,** 194-201.

BENNETT, P., PHELPS, C., BRAIN, K., HOOD, K. & GRAY, J. 2007. A randomized controlled trial of a brief self-help coping intervention designed to reduce distress when awaiting genetic risk information. *Journal of Psychosomatic Research,* 63**,** 59-64.

BENNETT, P., PHELPS, C., HILGART, J., HOOD, K., BRAIN, K. & MURRAY, A. 2012. Concerns and coping during cancer genetic risk assessment. *Psycho-Oncology,* 21**,** 611-617.

BERNIER, J. & POORTMANS, P. 2015. Clinical relevance of normal and tumour cell radiosensitivity in BRCA1/BRCA2 mutation carriers: A review. *Breast,* 24**,** 100-106.

BERNSTEIN, J. L., THOMAS, D. C., SHORE, R. E., ROBSON, M., BOICE, J. D., JR., STOVALL, M., ANDERSSON, M., BERNSTEIN, L., MALONE, K. E., REINER, A. S., LYNCH, C. F., CAPANU, M., SMITH, S. A., TELLHED, L., TERAOKA, S. N., BEGG, C. B., OLSEN, J. H., MELLEMKJAER, L., LIANG, X., DIEP, A. T., BORG, A., CONCANNON, P. & HAILE, R. W. 2013. Contralateral breast cancer after radiotherapy among BRCA1 and BRCA2 mutation carriers: a WECARE study report. *Eur J Cancer,* 49**,** 2979-85.

BLAIKIE, N. 2007. *Approaches to Social Inquiry,* Cambridge, Polity Press.

BLEIKER, E. M. A., AARONSON, N. K., MENKO, F. H., HAHN, D. E. E., VAN ASPEREN, C. J., RUTGERS, E. J. T., TEN KATE, L. P. & LESCHOT, N. J. 1997. Genetic counseling for hereditary cancer: a pilot study on experiences of patients and family members. *Patient Education & Counseling,* 32**,** 107-116.

BLOSS, C. S., MADLENSKY, L., SCHORK, N. J. & TOPOL, E. J. 2011. Genomic information as a behavioral health intervention: can it work? *Personalized Medicine,* 8**,** 659-667.

BOMBARD, Y., ROZMOVITS, L., TRUDEAU, M. E., LEIGHL, N. B., DEAL, K. & MARSHALL, D. A. 2014. *Patients' perceptions of gene expression profiling in breast cancer treatment decisions*.

BORDELEAU, L., PANCHAL, S. & GOODWIN, P. 2010. Prognosis of BRCA-associated breast cancer: A summary of evidence. *Breast Cancer Research And Treatment,* 119**,** 13-24.

BOWEN, M. 1978. *Family Therapy in Clinical Practice. New York,* New York, Jason Aaronson.

BOYLE, P. 2012. Triple-negative breast cancer: epidemiological considerations and recommendations. *Annals of Oncology,* 23**,** vi7-vi12.

BREASTCANCERCARE. 2014. *Referral to a Breast Clinic* [Online]. Breast Cancer Care. Available: http://www.breastcancercare.org.uk/breast-cancer-information/breast-awareness/referral-breast-clinic [Accessed 29/09/2014 2014].

BREASTCANCERLINKAGECONSORTIUM 1999. Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst,* 91**,** 1310-6.

BREKELMANS, C. T. M., TILANUS-LINTHORST, M. M. A., SEYNAEVE, C., VD OUWELAND, A., MENKE-PLUYMERS, M. B. E., BARTELS, C. C. M., KRIEGE, M., VAN GEEL, A. N., BURGER, C. W., EGGERMONT, A. M. M., MEIJERS-HEIJBOER, H. & KLIJN, J. G. M. 2007. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. *European Journal of Cancer,* 43**,** 867-876.

BRUNET, J.-S., GHADIRIAN, P., REBBECK, T. R., LERMAN, C., GARBER, J. E., TONIN, P. N., ABRAHAMSON, J., FOULKES, W. D., DALY, M., WAGNER-COSTALAS, J., GODWIN, A., OLOPADE, O. I., MOSLEHI, R., LIEDE, A., FUTREAL, P. A., WEBER, B. L., LENOIR, G. M., LYNCH, H. T. & NAROD, S. A. 1998. Effect of Smoking on Breast Cancer in Carriers of Mutant BRCA1 or BRCA2 Genes. *Journal of the National Cancer Institute,* 90**,** 761-765.

BRYMAN, A. 1988. *Quality and Quantity in Social Research Methods,* London, Unwin Hyman.

BRYMAN, A. 2012. *Social Research Methods,* Oxford, Oxford University Press.

BURCHER, S., MEISER, B., MITCHELL, G., SAUNDERS, C., RAHMAN, B., TUCKER, K., BARLOW-STEWART, K., WATTS, K., GLEESON, M. & KIRK, J. 2013. Oncology health professionals' attitudes toward treatment-focused genetic testing for women newly diagnosed with breast cancer. *Personalized Medicine,* 10**,** 431-440.

BURKE, W. & PRESS, N. 2006. Ethical obligations and counseling challenges in cancer genetics. *Journal Of The National Comprehensive Cancer Network: JNCCN,* 4**,** 185-191.

BURNS, H. 2009. Cancer Genetic Services in Scotland: Management of Women with a Family History of Breast Cancer *In:* DIVISION, H. P. (ed.). Edinburgh: The Scottish Government.

BYRSKI, T., DENT, R., BLECHARZ, P., FOSZCZYNSKA-KLODA, M., GRONWALD, J., HUZARSKI, T., CYBULSKI, C., MARCZYK, E., CHRZAN, R., EISEN, A., LUBINSKI, J. & NAROD, S. A. 2012. Results of a phase II open-label, non-randomized trial of cisplatin chemotherapy in patients with BRCA1-positive metastatic breast cancer. *Breast Cancer Res,* 14**,** R110.

BYRSKI, T., GRONWALD, J., HUZARSKI, T., GRZYBOWSKA, E., BUDRYK, M., STAWICKA, M., MIERZWA, T., SZWIEC, M., WISNIOWSKI, R., SIOLEK, M.,

DENT, R., LUBINSKI, J. & NAROD, S. 2010. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *J Clin Oncol,* 28**,** 375-9.

CANCERRESEARCHUK. 2012. *Tracking down the BRCA genes (Part 2)* [Online]. London: CancerReseachUK. Available: http://scienceblog.cancerresearchuk.org/2012/02/29/high-impact-science-tracking-down-the-brca-genes-part-2/ [Accessed 24/11/2014 2014].

CANCERRESEARCHUK. 2013. *Breast Cancer Survial Statistics* [Online]. London: CRUK. Available: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/survival/breast-cancer-survival-statistics [Accessed 26/11/2014 2014].

CANCERRESEARCHUK. 2014. *Breast Cancer* [Online]. Available: http://publications.cancerresearchuk.org/downloads/product/CS_KF_BREAST.pdf.

CANCERRESEARCHUK. Feb 2011. *Breast cancer - UK incidence statistics* [Online]. Cancer Research UK. Available: http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/.

CAPPELLETTI, V., VENERONI, S., CORADINI, D., ORIANA, S., TOMASIC, G., YOUNES, M. & DAIDONE, M. G. 2003. Re: Tamoxifen may be an effective treatment for BRCA1-related breast cancer irrespective of estrogen receptor status.

CARTER, S. & HENDERSON, L. 2005. Approaches to Qualitative Data Collection in Social Science *In:* BOWLING, A. E., S (ed.) *Handbook of Health Research Methods: Investigation, Measurement and Analysis.* Maidenhead: Open University Press.

CGHFBG 2001. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease: Collaborative Group on Hormonal Factors in Breast Cancer. *The Lancet,* 358**,** 1389-1399.

CHAN, I. S. & GINSBURG, G. S. 2011. Personalized medicine: Progress and promise. *Annual Review of Genomics and Human Genetics.*

CHAPPUIS, P. O., GOFFIN, J., WONG, N., PERRET, C., GHADIRIAN, P., TONIN, P. N. & FOULKES, W. D. 2002. A significant response to neoadjuvant chemotherapy in BRCA1/2 related breast cancer. *Journal of Medical Genetics,* 39**,** 608-610.

CHAPPUIS, P. O., ROSENBLATT, J. & FOULKES, W. D. 1999. The influence of familial and hereditary factors on the prognosis of breast cancer. *Annals of Oncology,* 10**,** 1163-1170.

CHEON, J. Y., MOZERSKY, J. & COOK-DEEGAN, R. 2014. Variants of uncertain significance in BRCA: a harbinger of ethical and policy issues to come? *Genome Medicine,* 6**,** 121.

CHEUNG, E. L., OLSON, A. D., YU, T. M., HAN, P. Z. & BEATTIE, M. S. 2010. Communication of BRCA Results and Family Testing in 1,103 High-Risk Women. *Cancer Epidemiology Biomarkers & Prevention,* 19**,** 2211-2219.

CHRISTINAT, A., DI LASCIO, S. & PAGANI, O. 2013. Hormonal therapies in young breast cancer patients: when, what and for how long? *Journal of Thoracic Disease,* 5**,** S36-S46.

CLARKE, S., BUTLER, K. & ESPLEN, M. J. 2008. The phases of disclosing BRCA1/2 genetic information to offspring. *Psycho-Oncology,* 17**,** 797-803.

CLAUS, E. B., SCHILDKRAUT, J. M., THOMPSON, W. D. & RISCH, N. J. 1996. The genetic attributable risk of breast and ovarian cancer. *Cancer,* 77**,** 2318.

COHEN, M. J. 2013. Overcoming barriers in the implementation of personalized medicine into clinical practice. *The Israel Medical Association journal,* 15**,** 599-601.

COLDITZ, G. A. & BOHLKE, K. 2014. Priorities for the primary prevention of breast cancer. *CA Cancer J Clin,* 64**,** 186-94.

COLE, M. P., JONES, C. T. & TODD, I. D. 1971. A new anti-oestrogenic agent in late breast cancer. An early clinical appraisal of ICI46474. *British Journal of Cancer,* 25**,** 270-275.

COOPER, B. T., MURPHY, J. O., SACCHINI, V. & FORMENTI, S. C. 2013. Local approaches to hereditary breast cancer. *Annals of Oncology,* 24**,** viii54-viii60.

CORNETTA, K. & BROWN, C. G. 2013. Balancing personalized medicine and personalized care. *Academic Medicine,* 88**,** 309-313.

COUCH, F. J., CERHAN, J. R., VIERKANT, R. A., GRABRICK, D. M., THERNEAU, T. M., PANKRATZ, V. S., HARTMANN, L. C., OLSON, J. E., VACHON, C. M. & SELLERS, T. A. 2001. Cigarette Smoking Increases Risk for Breast Cancer in High-Risk Breast Cancer Families. *Cancer Epidemiology Biomarkers & Prevention,* 10**,** 327-332.

COUCH, F. J., NATHANSON, K. L. & OFFIT, K. 2014. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. *Science (New York, N.Y.),* 343**,** 1466-1470.

CRESWELL, J. W. 2003. Research Design: Qualitative, Quantitative and Mixed Methods Approaches 2nd ed.

CRISCITIELLO, C., FUMAGALLI, D., SAINI, K. S. & LOI, S. 2010. Tamoxifen in early-stage estrogen receptor-positive breast cancer: overview of clinical use and molecular biomarkers for patient selection. *Oncotargets And Therapy,* 4**,** 1-11.

CROWE, M. 2005. Discourse analysis: towards an understanding of its place in nursing. *Journal of Advanced Nursing,* 51**,** 55-63.

CULVER, J. O., BRINKERHOFF, C. D., CLAGUE, J., YANG, K., SINGH, K. E., SAND, S. R. & WEITZEL, J. N. 2013. Variants of uncertain significance in BRCA testing: evaluation of surgical decisions, risk perception, and cancer distress. *Clin Genet,* 84**,** 464-72.

CUMMINGS, S. 2000. The Genetic Testing Process: How Much Counseling Is Needed? *Journal of Clinical Oncology,* 18**,** 60-64.

CYBULSKI, C., NAZARALI, S. & NAROD, S. A. 2014. Multiple primary cancers as a guide to heritability. *International Journal of Cancer,* 135**,** 1756-1763.

DA SILVA, L. & LAKHANI, S. R. 2010. Pathology of hereditary breast cancer. *Modern Pathology,* 23**,** S46-S51.

DALY, M. B. 2004. Tailoring breast cancer treatment to genetic status: The challenges ahead. *Journal of Clinical Oncology,* 22**,** 1776-1777.

DECRUYENAERE, M., EVERS-KIEBOOMS, G., BOOGAERTS, A., PHILIPPE, K., DEMYTTENAERE, K., DOM, R., VANDENBERGHE, W. & FRYNS, J. P. 2007. The complexity of reproductive decision-making in asymptomatic carriers of the Huntington mutation. *Eur J Hum Genet,* 15**,** 453-62.

DEFRANK, J. T., CAREY, L. A. & BREWER, N. T. 2013. Understanding how breast cancer patients use risk information from genomic tests. *Journal of Behavioral Medicine,* 36**,** 567-573.

DENT, R., TRUDEAU, M., PRITCHARD, K. I., HANNA, W. M., KAHN, H. K., SAWKA, C. A., LICKLEY, L. A., RAWLINSON, E., SUN, P. & NAROD, S. A. 2007. Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence. *Clinical Cancer Research,* 13**,** 4429-4434.

DENZIN, N. & LINCOLN, Y. 2005. The discipline and practice of qualitative research. *In:* DENZON, N. & LINCOLN, Y. (eds.) *Strategies of qualitative inquiry.* Thousand Oaks: Sage.

DERUIJTER, T. C., VEECK, J., DEHOON, J. P. J., VANENGELAND, M. & TJAN-HEIJNEN, V. C. 2011. Characteristics of triple-negative breast cancer.

DONNELLY, L. S., WATSON, M., MOYNIHAN, C., BANCROFT, E., EVANS, D. G. R., EELES, R., LAVERY, S. & ORMONDROYD, E. 2013. Reproductive decision-making in young female carriers of a BRCA mutation. *Human Reproduction,* 28**,** 1006-1012.

DORVAL, M., BOUCHARD, K., MAUNSELL, E., PLANTE, M., CHIQUETTE, J., CAMDEN, S., DUGAS, M. J., SIMARD, J., BESSETTE, P., BRIDGE, P., PROVENCHER, L., FRANCINE, D., KNOPPERS, B. M., LAFRAMBOISE, R., LESPÉRANCE, B., PICHETTE, R., LÉPINE, J. & VOYER, P. 2008. Health behaviors and psychological distress in women initiating BRCA1/2 genetic testing: Comparison with control population. *Journal of Genetic Counseling,* 17**,** 314-326.

DOUGALL, A. L., SMITH, A. W., SOMERS, T. J., POSLUSZNY, D. M., RUBINSTEIN, W. S. & BAUM, A. 2009. Coping with genetic testing for breast cancer susceptibility. *Psychosomatic Medicine,* 71**,** 98-105.

DOUGLAS, H. A., HAMILTON, R. J. & GRUBS, R. E. 2009. The effect of BRCA gene testing on family relationships: A Thematic Analysis of Qualitative Interviews. *Journal of Genetic Counseling,* 18**,** 418-435.

DOWDEN, B. & SWARTZ, N. *Truth* [Online]. The Internet Encyclopedia of Philosophy. Available: http://www.iep.utm.edu/truth/ [Accessed 14/03/2014 2014].

DUNNE, C. 2011. The place of the literature review in grounded theory research. *International Journal of Social Research Methodology,* 14**,** 111-124.

EASTON, D. F. 1999. How many more breast cancer predisposition genes are there? . *Cancer Research Campaign (CRC), Cambridge, UK*.

EASTON, D. F., FORD, D. & BISHOP, D. T. 1995. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *American journal of human genetics,* 56**,** 265.

EBCTCG 1998. Polychemotherapy for early breast cancer: an overview of the randomised trials: Early Breast Cancer Trialists' Collaborative Group. *The Lancet,* 352**,** 930-942.

EBCTCG 2005a. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials: Early Breast Cancer Trialists' Collaborative Group. *The Lancet,* 365**,** 1687-1717.

EBCTCG 2005b. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials: Early Breast Cancer Trialists' Collaborative Group. *Lancet,* 366**,** 2087-2106.

EBCTCG 2011. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised

trials: Early Breast Cancer Trialists' Collaborative Group. *The Lancet,* 378**,** 771-784.

EBCTCG 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials: Early Breast Cancer Trialists' Collaborative Group *The Lancet,* 379**,** 432-444.

ECCLES, D. M., EVANS, D. G. R. & MACKAY, J. 2000. Guidelines for a genetic risk based approach to advising women with a family history of breast cancer. *Journal of Medical Genetics,* 37**,** 203-209.

ECCLES, D. M., MITCHELL, G., MONTEIRO, A. N., SCHMUTZLER, R., COUCH, F. J., SPURDLE, A. B. & GOMEZ-GARCIA, E. B. 2015. BRCA1 and BRCA2 genetic testing-pitfalls and recommendations for managing variants of uncertain clinical significance. *Ann Oncol*.

ECCLES, D. M. & PICHERT, G. 2005. Familial non-BRCA1/BRCA2-associated breast cancer. *The Lancet Oncology,* 6**,** 705-711.

ECCLES, S. A., ABOAGYE, E. O., ALI, S., ANDERSON, A. S., ARMES, J., BERDITCHEVSKI, F., BLAYDES, J. P., BRENNAN, K., BROWN, N. J., BRYANT, H. E., BUNDRED, N. J., BURCHELL, J. M., CAMPBELL, A. M., CARROLL, J. S., CLARKE, R. B., COLES, C. E., COOK, G. J., COX, A., CURTIN, N. J., DEKKER, L. V., SILVA IDOS, S., DUFFY, S. W., EASTON, D. F., ECCLES, D. M., EDWARDS, D. R., EDWARDS, J., EVANS, D., FENLON, D. F., FLANAGAN, J. M., FOSTER, C., GALLAGHER, W. M., GARCIA-CLOSAS, M., GEE, J. M., GESCHER, A. J., GOH, V., GROVES, A. M., HARVEY, A. J., HARVIE, M., HENNESSY, B. T., HISCOX, S., HOLEN, I., HOWELL, S. J., HOWELL, A., HUBBARD, G., HULBERT-WILLIAMS, N., HUNTER, M. S., JASANI, B., JONES, L. J., KEY, T. J., KIRWAN, C. C., KONG, A., KUNKLER, I. H., LANGDON, S. P., LEACH, M. O., MANN, D. J., MARSHALL, J. F., MARTIN, L., MARTIN, S. G., MACDOUGALL, J. E., MILES, D. W., MILLER, W. R., MORRIS, J. R., MOSS, S. M., MULLAN, P., NATRAJAN, R., O'CONNOR, J. P., O'CONNOR, R., PALMIERI, C., PHAROAH, P. D., RAKHA, E. A., REED, E., ROBINSON, S. P., SAHAI, E., SAXTON, J. M., SCHMID, P., SMALLEY, M. J., SPEIRS, V., STEIN, R., STINGL, J., STREULI, C. H., TUTT, A. N., VELIKOVA, G., WALKER, R. A., WATSON, C. J., WILLIAMS, K. J., YOUNG, L. S. & THOMPSON, A. M. 2013. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. *Breast Cancer Res,* 15**,** R92.

EGGINGTON, J., BURBRIDGE, L., ROA, B., PRUSS, D., BOWLES, K., ROSENTHAL, E., ESTERLING, L. & WENSTRUP, R. Current variant of uncertain significance rates in BRCA1/2 and Lynch syndrome testing (MLH1, MSH2, MSH6, PMS2, EpCam). Presented American College of medical genetics and genomics annual meeting, 2012.

EGGLESTONE, C., MORRIS, A. & O'BRIEN, A. 2013. Effect of Direct-to-Consumer Genetic Tests on Health Behaviour and Anxiety: A Survey of Consumers and Potential Consumers. *Journal of Genetic Counseling,* 22**,** 565-575.

EIJZENGA, W. 2014. Specific psychosocial issues of individuals undergoing genetic counseling for cancer - a literature review. *Journal of Genetic Counseling,* 23**,** 133.

EIJZENGA, W., BLEIKER, E. M. A., HAHN, D. E. E., KLUIJT, I., SIDHARTA, G. N., GUNDY, C. & AARONSON, N. K. 2014. Psychosocial Aspects of Hereditary Cancer (PAHC) questionnaire: development and testing of a screening

questionnaire for use in clinical cancer genetics. *Psycho-Oncology,* 23**,** 862-869.

EL-TAMER, M., RUSSO, D., TROXEL, A., BERNARDINO, L., MAZZIOTTA, R., ESTABROOK, A., DITKOFF, B.-A., SCHNABEL, F. & MANSUKHANI, M. 2004. Survival and Recurrence After Breast Cancer in BRCA1/2 Mutation Carriers. *Annals of Surgical Oncology,* 11**,** 157-164.

ELO, S., KÄÄRIÄINEN, M., KANSTE, O., PÖLKKI, T., UTRIAINEN, K. & KYNGÄS, H. 2014. *Qualitative Content Analysis*.

ENNIS, C. 2012. Genetic screening: curiosity killed the CATG *The Guardian*, 11/10/2012.

ETCHEGARY, H., MILLER, F., DELAAT, S., WILSON, B., CARROLL, J. & CAPPELLI, M. 2009. Decision-making about inherited cancer risk: exploring dimensions of genetic responsibility. *Journal of Genetic Counseling,* 18**,** 252-264.

EUHUS, D. & ROBINSON, L. 2012. Genetic Counseling and Genetic Testing in the Preoperative Evaluation of Breast Cancer Patients. *Current Breast Cancer Reports,* 4**,** 102-109.

EUHUS, D. M. 2011. New insights into the prevention and treatment of familial breast cancer. *Journal of Surgical Oncology,* 103**,** 294-298.

EVANS, D. G., INGHAM, S., BAILDAM, A., ROSS, G., LALLOO, F., BUCHAN, I. & HOWELL, A. 2013. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. *Breast Cancer Research And Treatment,* 140**,** 135-142.

EVANS, D. G., SHENTON, A., WOODWARD, E., LALLOO, F., HOWELL, A. & MAHER, E. R. 2008. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer,* 8**,** 155.

EVANS, D. G. R., BARWELL, J., ECCLES, D. M., COLLINS, A., IZATT, L., JACOBS, C., DONALDSON, A., BRADY, A. F., CUTHBERT, A., HARRISON, R., THOMAS, S., HOWELL, A., MIEDZYBRODZKA, Z. & MURRAY, A. 2014. The Angelina Jolie effect: How high celebrity profile can have a major impact on provision of cancer related services. *Breast Cancer Research,* 16.

EVANS, D. G. R., LALLOO, F., HOPWOOD, P., MAURICE, A., BAILDAM, A., BRAIN, A., BARR, L. & HOWELL, A. 2005. Surgical decisions made by 158 women with hereditary breast cancer aged <50 years. *European Journal Of Surgical Oncology: The Journal Of The European Society Of Surgical Oncology And The British Association Of Surgical Oncology,* 31**,** 1112-1118.

FARMER, H., MCCABE, N., LORD, C. J., TUTT, A. N. J., JOHNSON, D. A., RICHARDSON, T. B., SANTAROSA, M., DILLON, K. J., HICKSON, I., KNIGHTS, C., MARTIN, N. M. B., JACKSON, S. P., SMITH, G. C. M. & ASHWORTH, A. 2005. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature,* 434**,** 917-921.

FERLAY, J., SHIN, H.-R., BRAY, F., FORMAN, D., MATHERS, C. & PARKIN, D. M. 2010. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer,* 127**,** 2893-2917.

FERLAY, J., SOERJOMATARAM, I., ERVIK, M., DIKSHIT, R., ESER, S., MATHERS, C., REBELO, M., PARKIN, D. M., FORMAN, D. & BRAY, F. 2013. *Cancer Incidence and Mortality Worldwide: GLOBOCAN 2012* [Online]. Lyon, France: International Agency for Research on Cancer. Available:

http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx [Accessed 28/8/2015 2015].

FINCH, A., METCALFE, K. A., CHIANG, J., ELIT, L., MCLAUGHLIN, J., SPRINGATE, C., ESPLEN, M. J., DEMSKY, R., MURPHY, J., ROSEN, B. & NAROD, S. A. 2013. The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. *Psycho-Oncology,* 22**,** 212-219.

FORD, D. & EASTON, D. F. 1995. The genetics of breast and ovarian cancer. *Br J Cancer,* 72**,** 805-12.

FORD, D., EASTON, D. F., BISHOP, D. T., NAROD, S. A. & GOLDGAR, D. E. 1994. Risks of cancer in BRCA1-mutation carriers. *The Lancet,* 343**,** 692-695.

FORD, D., EASTON, D. F., STRATTON, M., NAROD, S., GOLDGAR, D., DEVILEE, P., BISHOP, D. T., WEBER, B., LENOIR, G., CHANG-CLAUDE, J., SOBOL, H., TEARE, M. D., STRUEWING, J., ARASON, A., SCHERNECK, S., PETO, J., REBBECK, T. R., TONIN, P., NEUHAUSEN, S., BARKARDOTTIR, R., EYFJORD, J., LYNCH, H., PONDER, B. A. J., GAYTHER, S. A., BIRCH, J. M., LINDBLOM, A., STOPPA-LYONNET, D., BIGNON, Y., BORG, A., HAMANN, U., HAITES, N., SCOTT, R. J., MAUGARD, C. M., VASEN, H., SEITZ, S., CANNON-ALBRIGHT, L. A., SCHOFIELD, A. & ZELADA-HEDMAN, M. 1998. Genetic Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families. *The American Journal of Human Genetics,* 62**,** 676-689.

FORMENTI, S. C. & PRESTON-MARTIN, S. 2000. BRCA1/2 Germline Mutations: A Marker for Radioresistance or Radiosensitivity? *Journal of Clinical Oncology,* 18**,** 1159.

FORREST, K., SIMPSON, S. A., WILSON, B. J., VAN TEIJLINGEN, E. R., MCKEE, L., HAITES, N. & MATTHEWS, E. 2003. To tell or not to tell: barriers and facilitators in family communication about genetic risk. *Clinical Genetics,* 64**,** 317-326.

FORREST, P. 1987. *Breast Cancer Screening* [Online]. Available: http://www.cancerscreening.nhs.uk/breastscreen/publications/forrest-report.pdf.

FORTUNY, D., BALMAÑA, J., GRAÑA, B., TORRES, A., RAMÓN Y CAJAL, T., DARDER, E., GADEA, N., VELASCO, A., LÓPEZ, C., SANZ, J., ALONSO, C. & BRUNET, J. 2009. Opinion about reproductive decision making among individuals undergoing BRCA1/2 genetic testing in a multicentre Spanish cohort. *Human Reproduction (Oxford, England),* 24**,** 1000-1006.

FOSTER, C., EELES, R., ARDERN-JONES, A., MOYNIHAN, C. & WATSON, M. 2004. Juggling roles and expectations: dilemmas faced by women talking to relatives about cancer and genetic testing. *Psychology & Health,* 19**,** 439-455.

FOSTER, C., WATSON, M., EELES, R., ECCLES, D., ASHLEY, S., DAVIDSON, R., MACKAY, J., MORRISON, P. J., HOPWOOD, P. & EVANS, D. G. 2007. Predictive genetic testing for BRCA1/2 in a UK clinical cohort: three-year follow-up. *Br J Cancer,* 96**,** 718-24.

FOULKES, W. D., GOFFIN, J., BRUNET, J.-S., BÉGIN, L. R., WONG, N. & CHAPPUIS, P. O. 2002. Tamoxifen May Be an Effective Adjuvant Treatment for BRCA1-Related Breast Cancer Irrespective of Estrogen Receptor Status. *Journal of the National Cancer Institute,* 94**,** 1504-1506.

FOULKES, W. D., WONG, N., BRUNET, J.-S., BEGIN, L. R., ZHANG, J. C., MARTINEZ, J. J., ROZEN, F., TONIN, P. N., NAROD, S. A. & KARP, S. E.

1997. Germ-line BRCA1 mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer. *Clinical Cancer Research,* 3**,** 2465-2469.

FOURQUET, A., STOPPA-LYONNET, D., KIROVA, Y. M., SIGAL-ZAFRANI, B. & ASSELAIN, B. 2009. Familial breast cancer: Clinical response to induction chemotherapy or radiotherapy related to brca1/2 mutations status. *American Journal of Clinical Oncology: Cancer Clinical Trials,* 32**,** 127-131.

FRANCKEN, A. B., SCHOUTEN, P. C., BLEIKER, E. M. A., LINN, S. C. & RUTGERS, E. J. T. 2013. Breast cancer in women at high risk: The role of rapid genetic testing for BRCA1 and -2 mutations and the consequences for treatment strategies. *The Breast,* 22**,** 561-568.

FRIEBEL, T. M., DOMCHEK, S. M. & REBBECK, T. R. 2014. Modifiers of Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: A Systematic Review and Meta-Analysis. *Journal of the National Cancer Institute,* 106.

FUNG, B. 2013. Bowing again to the FDA, 23andMe stops issuing health-related genetic reports. *The Washington Post*, 6/12/2013.

GARCIA-ETIENNE, C. A., BARILE, M., GENTILINI, O. D., BOTTERI, E., ROTMENSZ, N., SAGONA, A., FARANTE, G., GALIMBERTI, V., LUINI, A., VERONESI, P. & BONANNI, B. 2009. Breast-conserving surgery in BRCA1/2 mutation carriers: Are we approaching an answer? *Annals of Surgical Oncology,* 16**,** 3380-3387.

GELLING, L. 2011. What is the difference between grounded theory and phenomenology? *Nursing Times,* 107**,** 25.

GENERALMEDICALCOUNCIL. 2009. *Confidentiality guidance: Genetic and other shared information* [Online]. London: GMC. Available: http://www.gmc-uk.org/guidance/ethical_guidance/confidentiality_67_69_genetic_and_other_shared_information.asp [Accessed 11/02/15 2015].

GHADIRIAN, P., NAROD, S., FAFARD, E., COSTA, M., ROBIDOUX, A. & NKONDJOCK, A. 2009. Breast cancer risk in relation to the joint effect of BRCA mutations and diet diversity. *Breast Cancer Res Treat,* 117**,** 417-22.

GINSBURG, G. S. & WILLARD, H. F. 2009. Genomic and personalized medicine: foundations and applications. *Translational Research,* 154**,** 277-287.

GLANZ, K. 1992. Factors associated with adherence to breast cancer screening among working women. *Journal of occupational medicine,* 34**,** 1071.

GLASER, B. & HOLTON, J. 2004. Remodeling Grounded Theory. *Forum: Qualitative Social Research,* 5.

GLASER, B. & STRAUSS, A. 1967. *The Discovery of Grounded Theory,* Chicago, Aldine.

GLASER, B. & STRAUSS, A. 1999. *The Discovery of Grounded Theory: Strategies for Qualitative Research,* London, AldineTransaction.

GOODWIN, P. J., PHILLIPS, K.-A., WEST, D. W., ENNIS, M., HOPPER, J. L., JOHN, E. M., O'MALLEY, F. P., MILNE, R. L., ANDRULIS, I. L., FRIEDLANDER, M. L., SOUTHEY, M. C., APICELLA, C., GILES, G. G. & LONGACRE, T. A. 2012. Breast Cancer Prognosis in BRCA1 and BRCA2 Mutation Carriers: An International Prospective Breast Cancer Family Registry Population-Based Cohort Study. *Journal of Clinical Oncology,* 30**,** 19-26.

GRACEFFA, A., M., R., VITA, G. L., TOSCANO, A., DATTOLA, R., MESSINA, C., VITA, G. & MAZZEO, A. 2009. Psychosocial impact of presymptomatic genetic testing for transthyretin amyloidotic polyneuropathy.

GRAESER, M. K., ENGEL, C., RHIEM, K., GADZICKI, D., BICK, U., KAST, K., FROSTER, U. G., SCHLEHE, B., BECHTOLD, A., ARNOLD, N., PREISLER-ADAMS, S., NESTLE-KRAEMLING, C., ZAINO, M., LOEFFLER, M., KIECHLE, M., MEINDL, A., VARGA, D. & SCHMUTZLER, R. K. 2009. Contralateral Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers. *Journal of Clinical Oncology,* 27**,** 5887-5892.

GRANT, A. M., VAN TEIJLINGEN, E. R., FORREST-KEENAN, K., TORRANCE, N., WILSON, B. J. & HAITES, N. E. 2006. Does breast cancer genetic counselling meet women's expectations? A qualitative study. *Critical Public Health,* 16**,** 281-293.

GRANT, R. W., JAMES, B. M., FLOREZ, J. C., PARK, E. R., GREEN, R. C., WAXLER, J. L., DELAHANTY, L. M. & O'BRIEN, K. E. 2011. Design of a randomized trial of diabetes genetic risk testing to motivate behavior change: The Genetic Counseling/Lifestyle Change (GC/LC) Study for Diabetes Prevention. *Clinical Trials,* 8**,** 609-615.

GRAVES, K. D., HAY, J. L. & O'NEILL, S. C. 2014. The promise of using personalized genomic information to promote behavior change: is the debate over, or just beginning? *Personalized Medicine,* 11**,** 173-185.

GREEN, J., RICHARDS, M., MURTON, F., STATHAM, H. & HALLOWELL, N. 1997. Family Communication and Genetic Counseling: The Case of Hereditary Breast and Ovarian Cancer. *Journal of Genetic Counseling,* 6**,** 45-60.

GRUBS, R., PARKER, L. & HAMILTON, R. 2014. Subtle Psychosocial Sequelae of Genetic Test Results. *Current Genetic Medicine Reports,* 2**,** 242-249.

GRYN, S. E. & KIM, R. B. 2014. Personalized medicine: Importance of clinical interpretative skills for real-world patient care. *Personalized Medicine,* 11**,** 395-408.

GUDMUNDSDOTTIR, K. & ASHWORTH, A. 2006. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene,* 25**,** 5864-5874.

GUINAN, E. M., HUSSEY, J., MCGARRIGLE, S. A., HEALY, L. A., O'SULLIVAN, J. N., BENNETT, K. & CONNOLLY, E. M. 2013a. A prospective investigation of predictive and modifiable risk factors for breast cancer in unaffected BRCA1 and BRCA2 gene carriers. *BMC Cancer,* 13**,** 138-138.

GUINAN, E. M., HUSSEY, J., MCGARRIGLE, S. A., HEALY, L. A., O'SULLIVAN, J. N., BENNETT, K. & CONNOLLY, E. M. 2013b. A prospective investigation of predictive and modifiable risk factors for breast cancer in unaffected BRCA1 and BRCA2 gene carriers. *BMC cancer,* 13**,** 138.

HAFFTY, B. G. 2002. Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. *Lancet,* 359**,** 1471.

HALLOWELL, N., FOSTER, C., EELES, R., ARDERN-JONES, A., MURDAY, V. & WATSON, M. 2003. Balancing autonomy and responsibility: the ethics of generating and disclosing genetic information. *Journal Of Medical Ethics,* 29**,** 74-79.

HAMBURG, M. A. & COLLINS, F. S. 2010. The Path to Personalized Medicine. *New England Journal of Medicine,* 363**,** 301-304.

HEATH, H. 2006. Exploring the influences and use of the literature during a grounded theory study. *Journal of Research in Nursing,* 11**,** 519-528.

HEEMSKERK-GERRITSEN, B. A. M., ROOKUS, M. A., AALFS, C. M., AUSEMS, M. G. E. M., COLLÉE, J. M., JANSEN, L., KETS, C. M., KEYMEULEN, K. B. M. I., KOPPERT, L. B., MEIJERS-HEIJBOER, H. E. J., MOOIJ, T. M.,

TOLLENAAR, R. A. E. M., VASEN, H. F. A., HEBON, HOONING, M. J. & SEYNAEVE, C. 2014. Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: A prospective analysis. *International Journal Of Cancer*.

HERNANDEZ, C. A. 2010. Getting grounded: using Glaserian grounded theory to conduct nursing research. *Can J Nurs Res,* 42**,** 150-63.

HICKEN, B. & TUCKER, D. 2002. Impact of genetic risk feedback: perceived risk and motivation for health protective behaviours. *Psychology, Health and Medicine,* 7**,** 25-36.

HODGSON, V. F., W & ENG, C & MAHER, E 2007. *Human Cancer Genetics: A Practical Guide to,* Cambridge, Cambridge University Press.

HOOD, L. & FRIEND, S. H. 2011. Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat Rev Clin Oncol,* 8**,** 184-7.

HOUSESOFPARLIMENT 2012. Consumer Genetic Testing. *In:* TECHNOLOGY, S. (ed.). London: UK Parliment.

HOWELL, A., ANDERSON, A. S., CLARKE, R. B., DUFFY, S. W., EVANS, D. G., GARCIA-CLOSAS, M., GESCHER, A. J., KEY, T. J., SAXTON, J. M. & HARVIE, M. N. 2014. Risk determination and prevention of breast cancer. *Breast Cancer Research,* 16**,** 446.

HU, F. B. 2011. Globalization of Diabetes: The role of diet, lifestyle, and genes. *Diabetes Care,* 34**,** 1249-1257.

HUBERT, A., MALI, B., HAMBURGER, T., ROTTENBERG, Y., UZIELY, B., PERETZ, T. & KADOURI, L. 2009. Response to neo-adjuvant chemotherapy in BRCA1 and BRCA2 related stage III breast cancer. *Familial Cancer,* 8**,** 173-177.

HUGHES, C., LERMAN, C., SCHWARTZ, M., PESHKIN, B. N., WENZEL, L., NAROD, S., CORIO, C., TERCYAK, K. P., HANNA, D., ISAACS, C. & MAIN, D. 2002. All in the family: evaluation of the process and content of sisters' communication about BRCA1 and BRCA2 genetic test results. *Am J Med Genet,* 107**,** 143-50.

HUZARSKI, T., BYRSKI, T., GRONWALD, J., GÓRSKI, B., DOMAGALA, P., CYBULSKI, C., OSZUREK, O., SZWIEC, M., GUGALA, K., STAWICKA, M., MORAWIEC, Z., MIERZWA, T., JANISZEWSKA, H., KILAR, E., MARCZYK, E., KOZAK-KLONOWSKA, B., SIOLEK, M., SURDYKA, D., WISNIOWSKI, R., POSMYK, M., SUN, P., LUBINSKI, J. & NAROD, S. A. 2013. Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 31**,** 3191-3196.

JACKSON, S. A., DAVIS, A. A., LI, J., YI, N., MCCORMICK, S. R., GRANT, C., FALLEN, T., CRAWFORD, B., LORANGER, K., LITTON, J., ARUN, B., VANDE WYDEVEN, K., SIDANI, A., FARMER, K., SANDERS, M., HOSKINS, K., NUSSBAUM, R., ESSERMAN, L., GARBER, J. E., KAKLAMANI, V. G. & THE NORTHWESTERN CANCER GENETICS, G. 2014. Characteristics of individuals with breast cancer rearrangements in BRCA1 and BRCA2. *Cancer,* 120**,** 1557-1564.

JACKSON, S. E. & CHESTER, J. D. 2014. Personalised cancer medicine. *International Journal Of Cancer. Journal International Du Cancer*.

JEFFERS, L., MORRISON, P. J., MCCAUGHAN, E. & FITZSIMONS, D. 2014. Maximising survival: The main concern of women with hereditary breast and

ovarian cancer who undergo genetic testing for BRCA1/2. *European Journal of Oncology Nursing,* 18**,** 411-418.

JOLY, Y., SAULNIER, K. M., OSIEN, G. & KNOPPERS, B. M. 2014. The ethical framing of personalized medicine. *Current Opinion in Allergy and Clinical Immunology,* 14**,** 404-408.

JULIAN-REYNIER, C., EISINGER, F., CHABAL, F., AURRAN, Y., BIGNON, Y. J., NOGUÈS, C., MACHELARD, M., MAUGARD, C., VENNIN, P. & SOBOL, H. 1998. Cancer genetic clinics: why do women who already have cancer attend? *European Journal of Cancer,* 34**,** 1549-1553.

JULIAN-REYNIER, C., EISINGER, F., CHABAL, F., LASSET, C., NOGUÈS, C., STOPPA-LYONNET, D., VENNIN, P. & SOBOL, H. 2000. Disclosure to the family of breast/ovarian cancer genetic test results: Patient's willingness and associated factors. *American Journal of Medical Genetics,* 94**,** 13-18.

KENEN, R., ARDERN-JONES, A. & EELES, R. 2006. "Social separation" among women under 40 years of age diagnosed with breast cancer and carrying a BRCA1 or BRCA2 mutation. *Journal of Genetic Counseling,* 15**,** 149-162.

KERLIKOWSKE, K., BROWN, J. S. & GRADY, D. G. 1992. Should Women with Familialy Ovarian Cancer Undergo Prophylactic Oophorectomy? *Obstetrics & Gynecology,* 80**,** 700-707.

KIBERSTIS, P. & ROBERTS, L. 2014. A Race Still Unfinished. *Science,* 343**,** 1451.

KING, M. C., MARKS, J. H. & MANDELL, J. B. 2003. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science,* 302**,** 643-6.

KIROVA, Y. M., SAVIGNONI, A., SIGAL-ZAFRANI, B., DE LA ROCHEFORDIERE, A., SALMON, R. J., THIS, P., ASSELAIN, B., STOPPA-LYONNET, D. & FOURQUET, A. 2010. Is the breast-conserving treatment with radiotherapy appropriate in BRCA1/2 mutation carriers? Long-term results and review of the literature. *Breast Cancer Research And Treatment,* 120**,** 119-126.

KLITZMAN, R. L. & SWEENEY, M. M. 2011. "In sickness and in health"? Disclosures of genetic risks in dating. *Journal of Genetic Counseling*.

KOCH, T. & HARRINGTON, A. 1998. Reconceptualizing rigour: the case for reflexivity. *J Adv Nurs,* 28**,** 882-90.

KOEHLY, L. M., PETERS, J. A., KUHN, N., HOSKINS, L., LETOCHA, A., KENEN, R., LOUD, J. & GREENE, M. H. 2008. Sisters in hereditary breast and ovarian cancer families: communal coping, social integration, and psychological well-being. *Psycho-Oncology,* 17**,** 812-821.

KORDE, L. A., MUELLER, C. M., LOUD, J. T., STRUEWING, J. P., NICHOLS, K., GREENE, M. H. & MAI, P. L. 2011. No evidence of excess breast cancer risk among mutation-negative women from BRCA mutation-positive families. *Breast Cancer Research And Treatment,* 125**,** 169-173.

KROMAN, N., HOLTVEG, H., WOHLFAHRT, J., JENSEN, M. B., MOURIDSEN, H. T., BLICHERT-TOFT, M. & MELBYE, M. 2004. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. *Cancer,* 100**,** 688-93.

LAKHANI, S. R. 1999. The pathology of familial breast cancer. Morphological aspects. *Breast Cancer Research,* 1**,** 31-35.

LAKHANI, S. R., VAN DE VIJVER, M. J., JACQUEMIER, J., ANDERSON, T. J., OSIN, P. P., MCGUFFOG, L. & EASTON, D. F. 2002. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2.

LARKIN, M., EATOUGH, V. & OSBORN, M. 2011. Interpretative phenomenological analysis and embodied, active, situated cognition. *Theory & Psychology,* 21**,** 318-337.

LEE, E. H., PARK, B., KIM, S.-W., LEE, M. H., AHN, S. H., SON, B. H., YOO, K.-Y. & KANG, D. 2010. Effect of BRCA1/2 mutation on short-term and long-term breast cancer survival: a systematic review and meta-analysis. *Breast Cancer Res Treat,* 122**,** 11-25.

LENFANT, C. 2013. Prospects of personalized medicine in cardiovascular diseases. *Metabolism,* 62 Suppl 1**,** S6-10.

LERMAN, C., CROYLE, R. T., TERCYAK, K. P. & HAMANN, H. 2002. Genetic testing: Psychological aspects and implications. *Journal of Consulting and Clinical Psychology,* 70**,** 784-797.

LERMAN, C., DALY, M., MASNY, A. & BALSHEM, A. 1994. Attitudes about genetic testing for breast-ovarian cancer susceptibility. *Journal of Clinical Oncology,* 12**,** 843-850.

LEWIS, J. & NICHOLLS, C. M. 2014. Design Issues. *In:* RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMISTON, R. (eds.) *Qualitative Research Practice: A Guide for Socisl Science Students & Researchers.* London: Sage.

LEWIS, J., RITCHIE, J., ORMISTON, R. & MORRELL, G. 2012. Generalising from Qualitative Research. *In:* RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMISTON, R. (eds.) *Qualitative Research Practice: A guide for social science students and researchers.* London: Sage.

LEWIS, M. A., MCBRIDE, C. M., POLLAK, K. I., PULEO, E., BUTTERFIELD, R. M. & EMMONS, K. M. 2006. Understanding health behavior change among couples: an interdependence and communal coping approach. *Soc Sci Med,* 62**,** 1369-80.

LIEBENS, F. P., CARLY, B., PASTIJN, A. & ROZENBERG, S. 2007. Management of BRCA1/2 associated breast cancer: A systematic qualitative review of the state of knowledge in 2006. *European Journal of Cancer,* 43**,** 238-257.

LIPS, E. H., MULDER, L., OONK, A., VAN DER KOLK, L. E., HOGERVORST, F. B. L., IMHOLZ, A. L. T., WESSELING, J., RODENHUIS, S. & NEDERLOF, P. M. 2013. Triple-negative breast cancer: BRCAness and concordance of clinical features with BRCA1-mutation carriers. *British Journal of Cancer,* 108**,** 2172-2177.

LITWINIUK, M. M., K, R., FILAS, V., ODLEWSKI, D. D., STAWICKA, M., KALETA, R. & BREBOROWICZ, J. 2008. Expression of estrogen receptor beta in the breast carcinoma of BRCA1 mutation carriers.

LODDER, L. N., FRETS, P. G., TRIJSBURG, R. W., MEIJERS-HEIJBOER, E. J., KLIJN, J. G., SEYNAEVE, C., VAN GEEL, A. N., TILANUS, M. M., BARTELS, C. C., VERHOOG, L. C., BREKELMANS, C. T., BURGER, C. W. & NIERMEIJER, M. F. 2002. One year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). *Breast Cancer Res Treat,* 73**,** 97-112.

LYNCH, H. T., ALBANO, W. A., DANES, B. S., LAYTON, M. A., KIMBERLING, W. J., LYNCH, J. F., CHENG, S. C., COSTELLO, K. A., MULCAHY, G. M. & WAGNER, C. A. 1984. Genetic predisposition to breast cancer. *Cancer,* 53**,** 612-622.

MACDONALD, D., SARNA, L., WEITZEL, J. & FERRELL, B. 2010. Women's Perceptions of the Personal and Family Impact of Genetic Cancer Risk

Assessment: Focus Group Findings. *Journal of Genetic Counseling,* 19**,** 148-160.
MACMILLAN. 2011. *What happens at the breast assessment clinic?* [Online]. London: MacMillan Cancer Support. Available: http://www.macmillan.org.uk/Cancerinformation/Testsscreening/Breastscreening/Assessmentclinics.aspx [Accessed 29/9/14 2014].
MACMILLAN. 2013. *Treating breast cancer in women - overview* [Online]. London: MacMillan Cancer Support. Available: http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Breast/Treatingbreastcancer/Treatmentoverview.aspx [Accessed 1/9/14 2014].
MALONE, K. E., DALING, J. R., THOMPSON, J. D., O'BRIEN, C. A., FRANCISCO, L. V. & OSTRANDER, E. A. 1998. Brca1 mutations and breast cancer in the general population: Analyses in women before age 35 years and in women before age 45 years with first-degree family history. *JAMA,* 279**,** 922-929.
MANNE, S., AUDRAIN, J., SCHWARTZ, M., MAIN, D., FINCH, C. & LERMAN, C. 2004. Associations between relationship support and psychological reactions of participants and partners to BRCA1 and BRCA2 testing in a clinic-based sample. *Ann Behav Med,* 28**,** 211-25.
MARCUS, J. N., WATSON, P., PAGE, D. L., NAROD, S. A., LENOIR, G. M., TONIN, P., LINDER-STEPHENSON, L., SALERNO, G., CONWAY, T. A. & LYNCH, H. T. 1996. Hereditary breast cancer: Pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. *Cancer,* 77**,** 697-709.
MARIOTTO, A., FEUER, E. J. & ABRAMS, J. 2003. RESPONSE: Re: Trends in Use of Adjuvant Multi-Agent Chemotherapy and Tamoxifen for Breast Cancer in the United States: 1975–1999. *Journal of the National Cancer Institute,* 95**,** 684-685.
MARIOTTO, A., FEUER, E. J., HARLAN, L. C., WUN, L.-M., JOHNSON, K. A. & ABRAMS, J. 2002. Trends in Use of Adjuvant Multi-Agent Chemotherapy and Tamoxifen for Breast Cancer in the United States: 1975–1999. *Journal of the National Cancer Institute,* 94**,** 1626-1634.
MARSH, D. J. & ZORI, R. T. 2002. Genetic insights into familial cancers - Update and recent discoveries. *Cancer Letters,* 181**,** 125-164.
MARTEAU, T. M. & LERMAN, C. 2001. Genetic risk and behavioural change. *BMJ : British Medical Journal,* 322**,** 1056-1059.
MARTEAU, T. M. & WEINMAN, J. 2006. Self-regulation and the behavioural response to DNA risk information: a theoretical analysis and framework for future research. *Soc Sci Med,* 62**,** 1360-8.
MCBRIDE, C. M., BRYAN, A. D., BRAY, M. S., SWAN, G. E. & GREEN, E. D. 2012. Health Behavior Change: Can Genomics Improve Behavioral Adherence? *American Journal of Public Health,* 102**,** 401-405.
MCBRIDE, C. M., KOEHLY, L. M., SANDERSON, S. C. & KAPHINGST, K. A. 2010. The Behavioral Response to Personalized Genetic Information: Will Genetic Risk Profiles Motivate Individuals and Families to Choose More Healthful Behaviors? *Annual Review of Public Health,* 31**,** 89-103.
MCCALLIN, A. 2003. Grappling with the literature in a grounded theory study. *Contemporary Nurse,* 15**,** 61-69.
MCDANIEL, S. H. 2005. The psychotherapy of genetics. *Family Process,* 44**,** 25-44.
MCGOWAN, M. L., SETTERSTEN, R. A., JUENGST, E. T. & FISHMAN, J. R. 2014. Integrating genomics into clinical oncology: Ethical and social challenges from

proponents of personalized medicine. *Urologic Oncology: Seminars and Original Investigations,* 32**,** 187-192.

MCGUIRE, V., JOHN, E. M., FELBERG, A., HAILE, R. W., BOYD, N. F., THOMAS, D. C., JENKINS, M. A., MILNE, R. L., DALY, M. B., WARD, J., TERRY, M. B., ANDRULIS, I. L., KNIGHT, J. A., GODWIN, A. K., GILES, G. G., SOUTHEY, M., WEST, D. W., HOPPER, J. L., WHITTEMORE, A. S. & INVESTIGATORS, K. 2006. No Increased Risk of Breast Cancer Associated with Alcohol Consumption among Carriers of BRCA1 and BRCA2 Mutations Ages <50 Years. *Cancer Epidemiology Biomarkers & Prevention,* 15**,** 1565-1567.

MEISER, B., GLEESON, M., KASPARIAN, N., BARLOW-STEWART, K., RYAN, M., WATTS, K., MENON, D., MITCHELL, G. & TUCKER, K. 2012a. There is no decision to make: Experiences and attitudes toward treatment-focused genetic testing among women diagnosed with ovarian cancer. *Gynecologic Oncology,* 124**,** 153-157.

MEISER, B., GLEESON, M., WATTS, K., PEATE, M., ZILLIACUS, E., BARLOW STEWART, K., SAUNDERS, C., MITCHELL, G. & KIRK, J. 2012b. Getting to the Point: What Women Newly Diagnosed With Breast Cancer Want to Know About Treatment-Focused Genetic Testing. *Oncology nursing forum,* 39**,** E101-E111.

MEISER, B., TUCKER, K., FRIEDLANDER, M., BARLOW-STEWART, K., LOBB, E., SAUNDERS, C. & MITCHELL, G. 2008. Genetic counselling and testing for inherited gene mutations in newly diagnosed patients with breast cancer: a review of the existing literature and a proposed research agenda. *Breast Cancer Research,* 10.

MELLON, S., GOLD, R., JANISSE, J., CICHON, M., TAINSKY, M. A., SIMON, M. S. & KORCZAK, J. 2008. Risk perception and cancer worries in families at increased risk of familial breast/ovarian cancer. *Psycho-Oncology,* 17**,** 756-766.

METCALFE, K., GERSHMAN, S., GHADIRIAN, P., LYNCH, H. T., SNYDER, C., TUNG, N., KIM-SING, C., EISEN, A., FOULKES, W. D., ROSEN, B., SUN, P. & NAROD, S. A. 2014. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. *British Medical Journal,* 348**,** g226.

METCALFE, K., GERSHMAN, S., LYNCH, H. T., GHADIRIAN, P., TUNG, N., KIM-SING, C., OLOPADE, O. I., DOMCHEK, S., MCLENNAN, J., EISEN, A., FOULKES, W. D., ROSEN, B., SUN, P. & NAROD, S. A. 2011. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *British Journal Of Cancer,* 104**,** 1384-1392.

METCALFE, K., LYNCH, H. T., GHADIRIAN, P., TUNG, N., OLIVOTTO, I., WARNER, E., OLOPADE, O. I., EISEN, A., WEBER, B., MCLENNAN, J., SUN, P., FOULKES, W. D. & NAROD, S. A. 2004. Contralateral Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. *Journal of Clinical Oncology,* 22**,** 2328-2335.

METCALFE, K. A., FOULKES, W. D., KIM-SING, C., AINSWORTH, P., ROSEN, B., ARMEL, S., POLL, A., EISEN, A., GILCHRIST, D., CHUDLEY, A., GHADIRIAN, P., MAUGARD, C., LEMIRE, E. G., SUN, P. & NAROD, S. A. 2008. Family history as a predictor of uptake of cancer preventive procedures by women with a BRCA1 or BRCA2 mutation. *Clin Genet,* 73**,** 474-9.

METCALFE, K. A., LIEDE, A., HOODFAR, E., SCOTT, A., FOULKES, W. D. & NAROD, S. A. 2000. An evaluation of needs of female BRCA1and BRCA2

carriers undergoing genetic counselling. *Journal of Medical Genetics,* 37**,** 866-874.
MIKI, Y. 1994. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science,* 266**,** 66.
MIKI, Y., SWENSEN, J., SHATTUCK-EIDENS, D., FUTREAL, P., HARSHMAN, K., TAVTIGIAN, S., LIU, Q., COCHRAN, C., BENNETT, L., DING, W. & ET, A. 1994. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science,* 266**,** 66-71.
MILES, M. B. & HUBERMAN, A. M. 1994. *Qualitative Data Analysis,* London, Sage.
MILLER, S. M. 1995. Monitoring versus blunting styles of coping with cancer influence the information patients want and need about their disease. Implications for cancer screening and management. *Cancer,* 76**,** 167-177.
MØLLER, P., HAGEN, A. I., APOLD, J., MAEHLE, L., CLARK, N., FIANE, B., LØVSLETT, K., HOVIG, E. & VABØ, A. 2007. Genetic epidemiology of BRCA mutations – family history detects less than 50% of the mutation carriers. *European Journal of Cancer,* 43**,** 1713-1717.
MOORMAN, P. G., IVERSEN, E. S., MARCOM, P. K., MARKS, J. R., WANG, F., LEE, E., URSIN, G., REBBECK, T. R., DOMCHEK, S. M., ARUN, B., SUSSWEIN, L., ISAACS, C., GARBER, J., VISVANATHAN, K., GRIFFIN, C. A., SUTPHEN, R., BRZOSOWICZ, J., GRUBER, S., FINKELSTEIN, D. M. & SCHILDKRAUT, J. M. 2010. Evaluation of established breast cancer risk factors as modifiers of BRCA1 or BRCA2: a multi-center case-only analysis. *Breast Cancer Research and Treatment,* 124**,** 441-451.
MURRAY, M. L., CERRATO, F., BENNETT, R. L. & JARVIK, G. P. 2011. Follow-up of carriers of BRCA1 and BRCA2 variants of unknown significance: variant reclassification and surgical decisions. *Genet Med,* 13**,** 998-1005.
NAROD, S. A., METCALFE, K., LYNCH, H. T., GHADIRIAN, P., ROBIDOUX, A., TUNG, N., GAUGHAN, E., KIM-SING, C., OLOPADE, O. I., FOULKES, W. D., ROBSON, M., OFFIT, K., JAKUBOWSKA, A., BYRSKI, T., HUZARSKI, T., SUN, P. & LUBINSKI, J. 2013. Should all BRCA1 mutation carriers with stage I breast cancer receive chemotherapy? *Breast Cancer Research And Treatment,* 138**,** 273-279.
NATIONALCANCERINSTITUTE. 2012. *Hormone Therapy for Breast Cancer* [Online]. National Institutes of Health. Available: http://www.cancer.gov/cancertopics/factsheet/Therapy/hormone-therapy-breast [Accessed 8/9/14 2014].
NATIONALHUMANGENOMERESEARCHINSTITUTE. 2014. *Proband* [Online]. National Institutes of Health. Available: http://www.genome.gov/glossary/index.cfm?id=164 [Accessed 9/6/14 2014].
NHSINFORM. *Breast Screening* [Online]. NHS Inform. Available: http://www.nhsinform.co.uk/Screening/breast.
NHSSCOTLAND 2008. Better Cancer Care, An Action Plan outlines the way forward for cancer services, which are required to support all those in Scotland who find themselves living with and beyond cancer. Edinburgh: The Scottish Government.
NHSSCOTLAND. 2009. *Breast cancer survival in Scotland* [Online]. Edinburgh ISD Scotland. Available: http://www.isdscotlandarchive.scot.nhs.uk/isd/1420.html#Cancerofthebreast 2012].

NHSTAYSIDE 2009. Breast Screening Service Three Yearly Report 2005-2008. Dundee: NHS Tayside.
NICE 2006. Familial breast cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care.
NICE 2009. Early and Locally Advanced Breast Cancer. Feb 2009 ed.
NICE 2013a. Evidence Review: Familial Breast Cancer. NICE.
NICE 2013b. Familial Breast Cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. *In:* NHS (ed.). Manchester: National Collaborating Centre for Cancer.
NICE 2013c. Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. London: National Institute for Health and Care Excellence.
NILSSON, M. P., HARTMAN, L., IDVALL, I., KRISTOFFERSSON, U., JOHANNSSON, O. T. & LOMAN, N. 2014. Long-term prognosis of early-onset breast cancer in a population-based cohort with a known BRCA1/2 mutation status. *Breast Cancer Research And Treatment,* 144**,** 133-142.
NKONDJOCK, A. & GHADIRIAN, P. 2004. Epidemiology of breast cancer among BRCA mutation carriers: an overview. *Cancer Lett,* 205**,** 1-8.
NKONDJOCK, A. & GHADIRIAN, P. 2007. Diet quality and BRCA-associated breast cancer risk. *Breast Cancer Res Treat,* 103**,** 361-9.
NKONDJOCK, A., ROBIDOUX, A., PAREDES, Y., NAROD, S. A. & GHADIRIAN, P. 2006. Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians. *Breast Cancer Res Treat,* 98**,** 285-94.
NOVAS, C. & ROSE, N. 2000. Genetic risk and the birth of the somatic individual. *Economy and Society,* 29**,** 485-513.
NYRHINEN, T., HIETALA, M., PUUKKA, P. & LEINO-KILPI, H. 2007. Privacy and equality in diagnostic genetic testing. *Nursing Ethics,* 14**,** 295-308.
O'DANIEL, J. M., HAGA, S. B. & WILLARD, H. F. 2010. Considerations for the Impact of Personal Genome Information: A Study of Genomic Profiling among Genetics and Genomics Professionals. *Journal of Genetic Counseling,* 19**,** 387-401.
ORMISTON, R., SPENCER, L., BARNARD, M. & SNAPE, D. 2014a. The Foundations of Qualitative Research. *In:* RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMISTON, R. (eds.) *Qualitative Research Practice: A Guide for Social Science Students & Researchers; 2nd Edition.* London: Sage.
ORMISTON, R., SPENCER, L., BARNARD, M. & SNAPE, D. 2014b. The Foundations of Qualitative Research in Qualitative Research in Practice *In:* RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMISTON, R. (eds.) *Qualitative Research in Practice.* London: Sage.
OXFORDENGLISHDICTIONARY *"attitude, n."*, Oxford University Press.
OXFORDENGLISHDICTIONARY *"opinion, n."*, Oxford University Press.
PAGANI, O., REGAN, M. M., WALLEY, B. A., FLEMING, G. F., COLLEONI, M., LÁNG, I., GOMEZ, H. L., TONDINI, C., BURSTEIN, H. J., PEREZ, E. A., CIRUELOS, E., STEARNS, V., BONNEFOI, H. R., MARTINO, S., GEYER, C. E., PINOTTI, G., PUGLISI, F., CRIVELLARI, D., RUHSTALLER, T., WINER, E. P., RABAGLIO-PORETTI, M., MAIBACH, R., RUEPP, B., GIOBBIE-HURDER, A., PRICE, K. N., BERNHARD, J., LUO, W., RIBI, K., VIALE, G., COATES, A. S., GELBER, R. D., GOLDHIRSCH, A. & FRANCIS, P. A. 2014.

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. *New England Journal of Medicine,* 371**,** 107-118.

PARTRIDGE, A. H., PAGANI, O., ABULKHAIR, O., AEBI, S., AMANT, F., AZIM, H. A., JR., COSTA, A., DELALOGE, S., FREILICH, G., GENTILINI, O. D., HARBECK, N., KELLY, C. M., LOIBL, S., MEIROW, D., PECCATORI, F., KAUFMANN, B. & CARDOSO, F. 2014. First international consensus guidelines for breast cancer in young women (BCY1). *The Breast,* 23**,** 209-220.

PASACRETA, J. V. 2003. Psychosocial issues associated with genetic testing for breast and ovarian cancer risk: an integrative review. *Cancer Invest,* 21**,** 588-623.

PASANISI, P., BRUNO, E., MANOUKIAN, S. & BERRINO, F. 2014. A randomized controlled trial of diet and physical activity in BRCA mutation carriers. *Familial Cancer,* 13**,** 181-187.

PATENAUDE, A., DEMARCO, T., PESHKIN, B., VALDIMARSDOTTIR, H., GARBER, J., SCHNEIDER, K., HEWITT, L., HAMILTON, J. & TERCYAK, K. 2013. Talking to Children About Maternal BRCA1/2 Genetic Test Results: A Qualitative Study of Parental Perceptions and Advice. *Journal of Genetic Counseling,* 22**,** 303-314.

PEASLAND, A., Z., W. L., ROWLING, E., KYLE, S., CHEN, T., HOPKINS, A., CLIBY, W. A., SARKARIA, J., BEALE, G., EDMONDSON, R. J. & CURTIN, N. J. 2011. Identification and evaluation of a potent novel ATR inhibitor, NU6027, in breast and ovarian cancer cell lines. *British Journal Of Cancer,* 105**,** 372-81.

PERSONALIZEDMEDICINECOALITION. 2014. *The Case for Personalized Medicine - 4th Edition* [Online]. Washington DC. Available: http://www.personalizedmedicinecoalition.org/Resources/The_Case_for_Personalized_Medicine [Accessed 19-01-2014 2014].

PETERS, G. J., VAN DER WILT, C. L., VAN MOORSEL, C. J. A., KROEP, J. R., BERGMAN, A. M. & ACKLAND, S. P. 2000. Basis for effective combination cancer chemotherapy with antimetabolites. *Pharmacology & Therapeutics,* 87**,** 227-253.

PETO, J., COLLINS, N., BARFOOT, R., SEAL, S., WARREN, W., RAHMAN, N., EASTON, D. F., EVANS, C., DEACON, J. & STRATTON, M. R. 1999. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. *Journal of the National Cancer Institute,* 91**,** 943-949.

PETTAPIECE-PHILLIPS, R., NAROD, S. & KOTSOPOULOS, J. 2015. The role of body size and physical activity on the risk of breast cancer in BRCA mutation carriers. *Cancer Causes & Control,* 26**,** 333-344.

PHAROAH, P. D. P., DAY, N. E., DUFFY, S., EASTON, D. F. & PONDER, B. A. J. 1997. Family history and the risk of breast cancer: A systematic review and meta-analysis. *International Journal of Cancer,* 71**,** 800-809.

PHELPS, C., BENNETT, P., HOOD, K., BRAIN, K. & MURRAY, A. 2013. A self-help coping intervention can reduce anxiety and avoidant health behaviours whilst waiting for cancer genetic risk information: results of a phase III randomised trial. *Psycho-Oncology,* 22**,** 837-844.

PHELPS, C., BENNETT, P., JONES, H., HOOD, K., BRAIN, K. & MURRAY, A. 2010. The development of a cancer genetic-specific measure of coping: the GRACE. *Psycho-Oncology,* 19**,** 847-854.

PHO, K., GELLER, A. & SCHROY, P. 2000. Lack of communication about familial colorectal cancer risk associated with colorectal adenomas (United States). *Cancer Causes & Control,* 11**,** 543-546.

PIERCE, L., PHILLIPS, K.-A., GRIFFITH, K., BUYS, S., GAFFNEY, D., MORAN, M., HAFFTY, B., BEN-DAVID, M., KAUFMAN, B., GARBER, J., MERAJVER, S., BALMAÑA, J., MEIROVITZ, A. & DOMCHEK, S. 2010. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. *Breast Cancer Research And Treatment,* 121**,** 389-398.

PIERCE, L. J. 2000. Effect of radiotherapy after breast-conserving treatment in women with breast cancer and germline BRCA1/2 mutations. *Journal of Clinical Oncology,* 18**,** 3360.

PIERCE, L. J., HUTCHINS, L. F., GREEN, S. R., LEW, D. L., GRALOW, J. R., LIVINGSTON, R. B., OSBORNE, C. K. & ALBAIN, K. S. 2005. Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology,* 23**,** 24-29.

PIERCE, L. J., LEVIN, A. M., REBBECK, T. R., BEN-DAVID, M. A., FRIEDMAN, E., SOLIN, L. J., HARRIS, E. E., GAFFNEY, D. K., HAFFTY, B. G., DAWSON, L. A., NAROD, S. A., OLIVOTTO, I. A., EISEN, A., WHELAN, T. J., OLOPADE, O. I., ISAACS, C., MERAJVER, S. D., WONG, J. S., GARBER, J. E. & WEBER, B. L. 2006. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology,* 24**,** 2437-2443.

PINKER, S. 2009. My genome, my self. *New York Times* 11 January 2009.

POLGAR, S. & THOMAS, S. A. 1995. Interview Techniques and the Analysis of Interview Data. *Introduction to Research in the Health Sciences.* 3rd ed. London: Churchill Livingstone.

PONDER, B. A. J., ANTONIOU, A., DUNNING, A., EAASTON, D. F. & PHAROAH, P. D. P. 2005. Polygenic Inherited Predisposition to Breast Cancer. *Cold Spring Harbor Symposia on Quantitative Biology,* 70**,** 35-41.

PRAVETTONI, G. & GORINI, A. 2011. A P5 cancer medicine approach: why personalized medicine cannot ignore psychology. *Journal of Evaluation in Clinical Practice,* 17**,** 594-596.

REIS, M. M., TAVAKOLI, M., DEWAR, J., GOUDIE, D., COOK, A., MCLEISH, L., YOUNG, D., KENYON, J. & STEEL, M. 2009. Evaluation of a surveillance programme for women with a family history of breast cancer. *Journal of Medical Genetics,* 46**,** 319-323.

RENNERT, G., BISLAND-NAGGAN, S., BARNETT-GRINESS, O., BAR-JOSEPH, N., ZHANG, S., RENNERT, H. S. & NAROD, S. A. 2007. Clinical Outcomes of Breast Cancer in Carriers of BRCA1 and BRCA2 Mutations. *New England Journal of Medicine,* 357**,** 115-123.

RHIEM, K., ENGEL, C., GRAESER, M., ZACHARIAE, S., KAST, K., KIECHLE, M., DITSCH, N., JANNI, W., MUNDHENKE, C., GOLATTA, M., VARGA, D., PREISLER-ADAMS, S., HEINRICH, T., BICK, U., GADZICKI, D., BRIEST, S., MEINDL, A. & SCHMUTZLER, R. K. 2012. The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study. *Breast Cancer Res,* 14**,** R156.

RIBNIKAR, D., RIBEIRO, J. M., PINTO, D., SOUSA, B., PINTO, A. C., GOMES, E., MOSER, E. C., CARDOSO, M. J. & CARDOSO, F. 2015. Breast cancer under age 40: a different approach. *Current Treatment Options In Oncology,* 16**,** 334-334.

RICHARDS, M. A. 2009. The National Awareness and Early Diagnosis Initiative in England: assembling the evidence. *Br J Cancer,* 101**,** S1-S4.

RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMISTON, R. (eds.) 2014. *Qualitative Research in Practive: A Guide for Social Science Students & Researchers,* London: Sage.

RITCHIE, J. & ORMISTON, R. 2014. The Applications of Qualtiative Methods to Social Research. *In:* RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMISTON, R. (eds.) *Qualitative Research Practice: A Guide for Social Science Students & Researchers.* London: Sage.

RITCHIE, J. & SPENCER, E. 1994. Qualitative Data Analysis for Applied Policy Research. *In:* BRYMAN, A. & BURGESS, R. G. (eds.) *Analysising Qualitative Data.* London: Routledge.

ROA, B. B., BOYD, A. A., VOLCIK, K. & RICHARDS, C. S. 1996. Ashkenazi jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nature Genetics,* 14**,** 185-187.

ROBERTSON, L., HANSON, H., SEAL, S., WARREN-PERRY, M., HUGHES, D., HOWELL, I., TURNBULL, C., HOULSTON, R., SHANLEY, S., BUTLER, S., EVANS, D. G., ROSS, G., ECCLES, D., TUTT, A. & RAHMAN, N. 2012. BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. *Br J Cancer,* 106**,** 1234-1238.

ROBSON, M. E., CHAPPUIS, P. O., SATAGOPAN, J., WONG, N., BOYD, J., GOFFIN, J. R., HUDIS, C., ROBERGE, D., NORTON, L., BEGIN, L. R., OFFIT, K. & FOULKES, W. D. 2004. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. *Breast Cancer Res,* 6**,** R8-R17.

RUBINSTEIN, W. 2008. Hereditary breast cancer: pathobiology, clinical translation, and potential for targeted cancer therapeutics. *Familial Cancer,* 7**,** 83-89.

SANDERSON, S. C. & WARDLE, J. 2005. Will genetic testing for complex diseases increase motivation to quit smoking? Anticipated reactions in a survey of smokers. *Health Education & Behavior: The Official Publication Of The Society For Public Health Education,* 32**,** 640-653.

SARANTAKOS, S. 1998a. *Social Research,* Basingstoke, Palgrave.

SARANTAKOS, S. 1998b. Varieties of Social Research. *Social Research.* 2 ed. Baisingstoke: Palgrave.

SAUNDERS, C., VIJAY, V., STEIN, J. & BAUM, M. 1999. Setting up a breast cancer family history clinic. *Annals Of The Royal College Of Surgeons Of England,* 81**,** 393-398.

SCHLICH-BAKKER, K. J., TEN KROODE, H. F. J., WÁRLÁM-RODENHUIS, C. C., VAN DEN BOUT, J. & AUSEMS, M. G. E. M. 2007. Barriers to participating in genetic counseling and BRCA testing during primary treatment for breast cancer. *Genetics In Medicine: Official Journal Of The American College Of Medical Genetics,* 9**,** 766-777.

SCHLICH-BAKKER, K. J., TENKROODE, H. F. J. & AUSEMS, M. G. E. M. 2006. A literature review of the psychological impact of genetic testing on breast cancer patients. *Patient Education and Counseling,* 62**,** 13-20.

SCHNEIDER, K. I. & SCHMIDTKE, J. 2014. Patient compliance based on genetic medicine: a literature review. *J Community Genet,* 5**,** 31-48.

SCHWARTZ, G. F., HUGHES, K. S., LYNCH, H. T., FABIAN, C. J., FENTIMAN, I. S., ROBSON, M. E., DOMCHEK, S. M., HARTMANN, L. C., HOLLAND, R., WINCHESTER, D. J. & AND THE CONSENSUS CONFERENCE, C. 2008. Proceedings of the International Consensus Conference on Breast Cancer Risk, Genetics, & Risk Management, April, 2007. *Cancer,* 113**,** 2627-2637.

SCHWARTZ, M. D. 2004. Impact of BRCA1/BRCA2 counseling and testing on newly diagnosed breast cancer patients. *Journal of Clinical Oncology,* 22**,** 1823.

SCHWARTZ, M. D. 2005. Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients. *Cancer epidemiology, biomarkers & prevention,* 14**,** 1003.

SCHWARTZ, M. D., KAUFMAN, E., PESHKIN, B. N., ISAACS, C., HUGHES, C., DEMARCO, T., FINCH, C. & LERMAN, C. 2003. Bilateral prophylactic oophorectomy and ovarian cancer screening following BRCA1/BRCA2 mutation testing. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology,* 21**,** 4034-4041.

SCHWARTZ, M. D., LERMAN, C., BROGAN, B., PESHKIN, B. N., HUGHES HALBERT, C., DEMARCO, T., LAWRENCE, W., MAIN, D., FINCH, C., MAGNANT, C., PENNANEN, M., TSANGARIS, T., WILLEY, S. & ISAACS, C. 2004. Impact of BRCA1/BRCA2 Counseling and Testing on Newly Diagnosed Breast Cancer Patients. *Journal of Clinical Oncology,* 22**,** 1823-1829.

SCHWARTZ, M. D., LERMAN, C., BROGAN, B., PESHKIN, B. N., ISAACS, C., DEMARCO, T., HALBERT, C. H., PENNANEN, M. & FINCH, C. 2005. Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients. *Cancer Epidemiology, Biomarkers & Prevention: A Publication Of The American Association For Cancer Research, Cosponsored By The American Society Of Preventive Oncology,* 14**,** 1003-1007.

SCOTTISHCANCERREGISTRY. 2010. *Trends in Caner Survival 1983-2007* [Online]. Edinburgh: NHS Scotland. Available: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Breast/ 2012].

SCOTTISHGOVERNMENT 2012a. Detect cancer early initiative. Edinburgh.

SCOTTISHGOVERNMENT 2012b. Scottish Index of Multiple Deprivations. Edinburgh.

SCOTTISHGOVERNMENT 2013. Breast cancer genetic testing. Edinburgh: The Scottish Government.

SERVICK, K. 2014. Breast Cancer: A World of Differences. *Science,* 343**,** 1452-1453.

SHIELDS, P. G. & HARRIS, C. C. 2000. Cancer Risk and Low-Penetrance Susceptibility Genes in Gene-Environment Interactions. *Journal of Clinical Oncology,* 18**,** 2309-2315.

SHILOH, S., KOEHLY, L., JENKINS, J., MARTIN, J. & HADLEY, D. 2008. Monitoring coping style moderates emotional reactions to genetic testing for hereditary nonpolyposis colorectal cancer: a longitudinal study. *Psychooncology,* 17**,** 746-55.

SHUEN, A. Y. & FOULKES, W. D. 2011. Inherited mutations in breast cancer genes - risk and response. *Journal Of Mammary Gland Biology And Neoplasia,* 16**,** 3-15.

SIGN 2005. Management of breast cancer in women: A national clinical guideline (SIGN 84). *In:* SCOTLAND, N. Q. I. (ed.). Edinburgh: NHS Scotland.

SIGN 2013. Treatment of Primary Breast Cancer: SIGN 134. *In:* SCOTLAND, H. I. (ed.). Edinburgh: Scottish Intercollegiate Guidelines Network

SILVERMAN, D. 2000. *Doing Qualitative Research: A Practical Handbook,* London, Sage.

SKIRTON, H., CORDIER, C., INGVOLDSTAD, C., TARIS, N. & BENJAMIN, C. 2014. The role of the genetic counsellor: a systematic review of research evidence. *Eur J Hum Genet*.

SMITH, A. W., DOUGALL, A. L., POSLUSZNY, D. M., SOMERS, T. J., RUBINSTEIN, W. S. & BAUM, A. 2008. Psychological distress and quality of life associated with genetic testing for breast cancer risk. *Psycho-Oncology,* 17**,** 767-773.

SMITH, I. E., DOWSETT, M., YAP, Y. S., WALSH, G., LONNING, P. E., SANTEN, R. J. & HAYES, D. 2006a. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. *J Clin Oncol,* 24**,** 2444-7.

SMITH, J., FLOWERS, P. & LARKIN, M. 2009. Interpretative Phoneomological Analysis: theory, method and research. London: SAGE Publications.

SMITH, K. L. & ISAACS, C. 2011. BRCA mutation testing in determining breast cancer therapy. *Cancer Journal,* 17**,** 492-499.

SMITH, P., MCGUFFOG, L., EASTON, D. F., MANN, G. J., PUPO, G. M., NEWMAN, B., CHENEVIX-TRENCH, G., SZABO, C., SOUTHEY, M., RENARD, H., ODEFREY, F., LYNCH, H., STOPPA-LYONNET, D., COUCH, F., HOPPER, J. L., GILES, G. G., MCCREDIE, M. R. E., BUYS, S., ANDRULIS, I., SENIE, R., GOLDGAR, D. E., OLDENBURG, R., KROEZE-JANSEMA, K., KRAAN, J., MEIJERS-HEIJBOER, H., KLIJN, J. G. M., VAN ASPEREN, C., VAN LEEUWEN, I., VASEN, H. F. A., CORNELISSE, C. J., DEVILEE, P., BASKCOMB, L., SEAL, S., BARFOOT, R., MANGION, J., HALL, A., EDKINS, S., RAPLEY, E., WOOSTER, R., CHANG-CLAUDE, J., ECCLES, D., EVANS, D. G., FUTREAL, P. A., NATHANSON, K. L., WEBER, B. L., RAHMAN, N. & STRATTON, M. R. 2006b. A genome wide linkage search for breast cancer susceptibility genes. *Genes, Chromosomes and Cancer,* 45**,** 646-655.

SMITH, S. A., FRENCH, T. & HOLLINGSWORTH, S. J. 2014. The impact of germline mutations on targeted therapy. *The Journal of Pathology,* 232**,** 230-243.

SONG, M., LEE, K.-M. & KANG, D. 2011. Breast cancer prevention based on gene-environment interaction. *Molecular Carcinogenesis,* 50**,** 280-290.

SOTIRIOU, C., NEO, S.-Y., MCSHANE, L. M., KORN, E. L., LONG, P. M., JAZAERI, A., MARTIAT, P., FOX, S. B., HARRIS, A. L. & LIU, E. T. 2003. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. *Proceedings of the National Academy of Sciences,* 100**,** 10393-10398.

SPENCER, L., RITCHIE, J., ORMISTON, R., O'CONNOR, W. & BARNARD, M. 2014. Analysis: Principles and Processes. *In:* RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMISTON, R. (eds.) *Qualitative Research in Practice: A Guide for Social Science Students & Researchers.* London: Sage.

SPURDLE, A. B., HEALEY, S., DEVEREAU, A., HOGERVORST, F. B., MONTEIRO, A. N., NATHANSON, K. L., RADICE, P., STOPPA-LYONNET, D.,

TAVTIGIAN, S., WAPPENSCHMIDT, B., COUCH, F. J. & GOLDGAR, D. E. 2012. ENIGMA--evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. *Hum Mutat,* 33**,** 2-7.

STERN, P. N. 2010. On Solid Ground Essential Properties for Growing. *In:* BRYANT, A. & CHARMAZ, K. (eds.) *Tha SAGE handbook of Grounded Theory.* Paperback ed.: SAGE.

STOPPA-LYONNET, D., ANSQUER, Y., DREYFUS, H., GAUTIER, C., GAUTHIER-VILLARS, M., BOURSTYN, E., CLOUGH, K. B., MAGDELÉNAT, H., POUILLART, P., VINCENT-SALOMON, A. & FOURQUET, A. 2000. Familial invasive breast cancers: Worse outcome related to BRCA1 mutations. *Journal of Clinical Oncology,* 18**,** 4053-4059.

STRATTON, M. R. 1997. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. *The Lancet,* 349**,** 1505-1510.

STRATTON, M. R. & RAHMAN, N. 2008. The emerging landscape of breast cancer susceptibility. *Nat Genet,* 40**,** 17-22.

STRAUSS, A. & CORBIN, J. 1998. *Basics of Qualitative Research: Techniques and Proceedures for Developing Grounded Theory,* London, Sage.

STRUEWING, J. P., HARTGE, P., WACHOLDER, S., BAKER, S. M., BERLIN, M., MCADAMS, M., TIMMERMAN, M. M., BRODY, L. C. & TUCKER, M. A. 1997. The Risk of Cancer Associated with Specific Mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *New England Journal of Medicine,* 336**,** 1401-1408.

SUTHERS, G. K., ARMSTRONG, J., MCCORMACK, J. & TROTT, D. 2006. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *Journal Of Medical Genetics,* 43**,** 665-670.

TAYLOR, C., MUNRO, A. J., GLYNNE-JONES, R., GRIFFITH, C., TREVATT, P., RICHARDS, M. & RAMIREZ, A. J. 2010. Multidisciplinary team working in cancer: what is the evidence? *BMJ (Clinical Research Ed.),* 340**,** c951-c951.

TERCYAK, K. P., LERMAN, C., PESHKIN, B. N., HUGHES, C., MAIN, D., ISAACS, C. & SCHWARTZ, M. D. 2001. Effects of coping style and BRCA1 and BRCA2 test results on anxiety among women participating in genetic counseling and testing for breast and ovarian cancer risk. *Health psychology,* 20**,** 217-222.

TERCYAK, K. P., MAYS, D., DEMARCO, T. A., PESHKIN, B. N., VALDIMARSDOTTIR, H. B., SCHNEIDER, K. A., GARBER, J. E. & PATENAUDE, A. F. 2013. Decisional Outcomes of Maternal Disclosure of BRCA1/2 Genetic Test Results to Children. *Cancer Epidemiology Biomarkers & Prevention,* 22**,** 1260-1266.

TERCYAK, K. P., PESHKIN, B. N., BROGAN, B. M., DEMARCO, T., PENNANEN, M. F., WILLEY, S. C., MAGNANT, C. M., ROGERS, S., ISAACS, C. & SCHWARTZ, M. D. 2007. Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology,* 25**,** 285-291.

THOMPSON, D. & EASTON, D. 2004. The genetic epidemiology of breast cancer genes. *Journal Of Mammary Gland Biology And Neoplasia,* 9**,** 221-236.

TISCHKOWITZ, M. D. & FOULKES, W. D. 2006. The basal phenotype of BRCA1-related breast cancer: past, present and future. *Cell Cycle (Georgetown, Tex.),* 5**,** 963-967.

TRAINER, A. H., LEWIS, C. R., TUCKER, K., MEISER, B., FRIEDLANDER, M. & WARD, R. L. 2010a. The role of BRCA mutation testing in determining breast cancer therapy. *Nat Rev Clin Oncol,* 7**,** 708-17.

TRAINER, A. H., MEISER, B., WATTS, K., MITCHELL, G., TUCKER, K. & FRIEDLANDER, M. 2010b. Moving Toward Personalized Medicine Treatment-Focused Genetic Testing of Women Newly Diagnosed With Ovarian Cancer. *International Journal of Gynecological Cancer,* 20**,** 704-716.

TRUNCELLITO, D. A. *Epistemology* [Online]. Internet Encyclopedia of Philosophy. Available: http://www.iep.utm.edu/soc-sci [Accessed 05/03/2014 2014].

TURNER, N. C. & TUTT, A. N. 2012. Platinum chemotherapy for BRCA1-related breast cancer: do we need more evidence? *Breast Cancer Res,* 14**,** 115.

UK, C. R. Feb 2011. *Breast cancer - UK incidence statistics* [Online]. Cancer Research UK. Available: http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/.

VALACHIS, A., NEARCHOU, A. D. & LIND, P. 2014. Surgical management of breast cancer in BRCA-mutation carriers: A systematic review and meta-analysis. *Breast Cancer Research And Treatment,* 144**,** 443-455.

VALVERDE, K. 2006. Why Me? Why Not Me? *Journal of Genetic Counseling,* 15**,** 461-463.

VAN DIJK, S., OTTEN, W., ZOETEWEIJ, M. W., TIMMERMANS, D. R., VAN ASPEREN, C. J., BREUNING, M. H., TOLLENAAR, R. A. & KIEVIT, J. 2003. Genetic counselling and the intention to undergo prophylactic mastectomy: effects of a breast cancer risk assessment. *Br J Cancer,* 88**,** 1675-81.

VAN DIJK, S., VAN ROOSMALEN, M. S., OTTEN, W. & STALMEIER, P. F. 2008. Decision making regarding prophylactic mastectomy: stability of preferences and the impact of anticipated feelings of regret. *J Clin Oncol,* 26**,** 2358-63.

VAN DRIEL, C. M., ELTAHIR, Y., DE VRIES, J., JASPERS, J. P., OOSTERWIJK, J. C., MOURITS, M. J. & DE BOCK, G. H. 2013. Risk-reducing mastectomy in BRCA1/2 mutation carriers: Factors influencing uptake and timing. *Maturitas,* 77**,** 180-184.

VAN OOSTROM, I., MEIJERS-HEIJBOER, H., DUIVENVOORDEN, H. J., BROCKER-VRIENDS, A. H., VAN ASPEREN, C. J., SIJMONS, R. H., SEYNAEVE, C., VAN GOOL, A. R., KLIJN, J. G., RIEDIJK, S. R., VAN DOOREN, S. & TIBBEN, A. 2007. A prospective study of the impact of genetic susceptibility testing for BRCA1/2 or HNPCC on family relationships. *Psychooncology,* 16**,** 320-8.

VERONESI, A., DE GIACOMI, C., MAGRI, M. D., LOMBARDI, D., ZANETTI, M., SCUDERI, C., DOLCETTI, R., VIEL, A., CRIVELLARI, D. & BIDOLI, E. 2005. Familial breast cancer: characteristics and outcome of BRCA 1–2 positive and negative cases. *BMC Cancer,* 5**,** 70.

VIG, H. S. & WANG, C. 2012. The evolution of personalized cancer genetic counseling in the era of personalized medicine. *Familial Cancer,* 11**,** 539-544.

WALSH, T., CASADEI, S., COATS, K. H., SWISHER, E., STRAY, S. M., HIGGINS, J., ROACH, K. C., MANDELL, J., LEE, M. K., CIERNIKOVA, S., FORETOVA, L., SOUCEK, P. & KING, M.-C. 2006. Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer. *JAMA: The Journal of the American Medical Association,* 295**,** 1379-1388.

WATSON, M., FOSTER, C., EELES, R., ECCLES, D., ASHLEY, S., DAVIDSON, R., MACKAY, J., MORRISON, P. J., HOPWOOD, P. & EVANS, D. G. R. 2004. Psychosocial impact of breast//ovarian (BRCA 1//2) cancer-predictive genetic testing in a UK multi-centre clinical cohort. *Br J Cancer,* 91**,** 1787-1794.

WATTS, K. J., MEISER, B., MITCHELL, G., KIRK, J., SAUNDERS, C., PEATE, M., DUFFY, J., KELLY, P. J., GLEESON, M., BARLOW-STEWART, K., RAHMAN, B., FRIEDLANDER, M. & TUCKER, K. 2012. How should we discuss genetic testing with women newly diagnosed with breast cancer? Design and implementation of a randomized controlled trial of two models of delivering education about treatment-focused genetic testing to younger women newly diagnosed with breast cancer. *BMC Cancer,* 12**,** 320-332.

WEITZEL, J. N. 2003. Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. *Archives of surgery,* 138**,** 1323.

WELDON, C. B., TROSMAN, J. R., GRADISHAR, W. J., BENSON, A. B. & SCHINK, J. C. 2012. Barriers to the Use of Personalized Medicine in Breast Cancer. *Journal of Oncology Practice,* 8**,** e24-e31.

WEVERS, M., AUSEMS, M., BLEIKER, E., RUTGERS, E., WITKAMP, A., HAHN, D., BROUWER, T., KUENEN, M., VAN DER SANDEN-MELIS, J., VAN DER LUIJT, R., HOGERVORST, F., VAN DALEN, T., THEUNISSEN, E., VAN OOIJEN, B., DE ROOS, M., BORGSTEIN, P., VROUENRAETS, B., HUISMAN, J., BOUMA, W., RIJNA, H., VENTE, J., VALDIMARSDOTTIR, H., VERHOEF, S. & AARONSON, N. 2012a. Rapid genetic counseling and testing in newly diagnosed breast cancer patients, findings from an RCT. *Cancer Research,* 72**,** P4-11-01.

WEVERS, M. R., AARONSON, N. K., VERHOEF, S., BLEIKER, E. M. A., HAHN, D. E. E., KUENEN, M. A., VAN DER SANDEN-MELIS, J., BROUWER, T., HOGERVORST, F. B. L., VAN DER LUIJT, R. B., VALDIMARSDOTTIR, H. B., VAN DALEN, T., THEUNISSEN, E. B. M., VAN OOIJEN, B., DE ROOS, M. A., BORGSTEIN, P. J., VROUENRAETS, B. C., VRIENS, E., BOUMA, W. H., RIJNA, H., VENTE, J. P., WITKAMP, A. J., RUTGERS, E. J. T. & AUSEMS, M. G. E. M. 2014. Impact of rapid genetic counselling and testing on the decision to undergo immediate or delayed prophylactic mastectomy in newly diagnosed breast cancer patients: findings from a randomised controlled trial. *Br J Cancer,* 110**,** 1081-1087.

WEVERS, M. R., AUSEMS, M. G. E. M., VERHOEF, S., BLEIKER, E. M. A., HAHN, D. E. E., HOGERVORST, F. B. L., VAN DER LUIJT, R. B., VALDIMARSDOTTIR, H. B., VAN HILLEGERSBERG, R., RUTGERS, E. J. & AARONSON, N. K. 2011a. Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: Design of a multicenter randomized clinical trial. *BMC Cancer,* 11.

WEVERS, M. R., AUSEMS, M. G. E. M., VERHOEF, S., BLEIKER, E. M. A., HAHN, D. E. E., HOGERVORST, F. B. L., VAN DER LUIJT, R. B., VALDIMARSDOTTIR, H. B., VAN HILLEGERSBERG, R., RUTGERS, E. J. T. H. & AARONSON, N. K. 2011b. Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: design of a multicenter randomized clinical trial. *BMC Cancer,* 11**,** 6-6.

WEVERS, M. R., HAHN, D. E. E., VERHOEF, S., BOLHAAR, M. D. K., AUSEMS, M. G. E. M., AARONSON, N. K. & BLEIKER, E. M. A. 2012b. Breast cancer genetic counseling after diagnosis but before treatment: A pilot study on

treatment consequences and psychological impact. *Patient Education and Counseling,* 89**,** 89-95.

WOOSTER, R. 1995. Identification of the breast cancer susceptibility gene BRCA2. *Nature,* 378**,** 789.

WOOSTER, R., BIGNELL, G., LANCASTER, J., SWIFT, S., SEAL, S., MANGION, J., COLLINS, N., GREGORY, S., GUMBS, C., MICKLEM, G., BARFOOT, R., HAMOUDI, R., PATEL, S., RICES, C., BIGGS, P., HASHIM, Y., SMITH, A., CONNOR, F., ARASON, A., GUDMUNDSSON, J., FICENEC, D., KELSELL, D., FORD, T. D., TIMOTHY BISHOP, D., SPURR, N. K., PONDER, B. A. J., EELES, R., PETO, J., DEVILEE, P., CORNELISSE, C., LYNCH, H., NAROD, S., LENOIR, G., EGILSSON, V., BJORK BARKADOTTIR, R., EASTON, D. F., BENTLEY, D. R., FUTREAL, P. A., ASHWORTH, A. & STRATTON, M. R. 1995. Identification of the breast cancer susceptibility gene BRCA2. *Nature,* 378**,** 789-792.

APPENDIX A. BREAST CANCER INCIDENCE

Worldwide breast cancer is the most common female cancer (Ferlay et al., 2010, Servick, 2014). Incidence has continued to rise since the 1970s. In the United Kingdom (UK) breast cancer since 1991 has been the most frequently diagnosed female cancer and currently accounts for 30% of all cancer in UK women (CancerResearchUK, Feb 2011). A woman in the general UK population carries a 1 in 8 risk for developing breast cancer (CancerResearchUK, Feb 2011).

UK and Scottish diagnosis rates for 2008 and 2011 are provided in Table 12. Significantly higher age-standardised rates were reported in 2011 for Scotland compared to England, Wales and Northern Ireland (CancerResearchUK, Feb 2011). Standardising diagnosis by age is appropriate when examining cancer rates because cancer diagnosis occurs more frequently in older age. Higher age-standardised rates indicate that across all ages a higher percentage or incidence was reported for the Scottish population. Despite a higher incidence in Scotland (2011) breast cancer was not the most common cancer; lung cancer in Scotland overtook breast cancer for the first time since 1997 (CancerResearchUK, Feb 2011).

Improving breast cancer outcomes with awareness and early diagnosis is a clinical priority for the UK (Richards, 2009) and Scottish Governments (NHSScotland, 2008, ScottishGovernment, 2012a).

Table 12: UK Breast Cancer Diagnosis

Year	UK	Scotland
2008	47,693	4,232
2011	49,936	5,578

Source (CancerResearchUK, Feb 2011)

Many scientific and health care advances have improved breast cancer detection and treatment since the 1970s furthermore mortality has consistently fallen since 1989 (CancerResearchUK, 2014). As is the case for all cancers, survival rates for breast cancer in developed countries are more favourable than in the developing world (Ferlay et al., 2010, Servick, 2014).

Regardless of survival rates death from breast cancer is still the most frequent cause of cancer death in women (Ferlay et al., 2010, Servick, 2014). In Scotland the relative five-year survival rates for women diagnosed with breast cancer between 2003 and 2007 reached 85.9% compared with only 65% twenty years earlier (NHSScotland, 2009, ScottishCancerRegistry, 2010) . These improvements are mirrored in England; five-year relative survival rates reached 85.1% for women diagnosed with breast cancer in 2005-2009 compared with only 52% thirty years earlier (UK, Feb 2011, CancerResearchUK, 2013). Despite survival rate improvements breast cancer remains the single most common cause of death among women aged 25-49 in the UK (CancerResearchUK, 2013).

APPENDIX B. BREAST CANCER SCREENING & DIAGNOSIS

The Forrest Committee advised that a national breast screening programme should be introduced with the aim of reducing breast cancer mortality by 25% by the year 2000 (Forrest, 1987). National Health Service Breast Screening Programme (NHSBSP) was initiated in 1988. The Scottish Breast Screening Programme (SBSP)[69] was fully operational from 1991, with the first round of screening completed by 1994.

Breast Screening Programmes aim to detect early breast cancer using mammograms and recommend for women:

- in the general population three-yearly mammograms from the age of 50-70
- with a moderate to high risk family history annual mammograms before age 40 and / or Magnetic Resonance Imaging (MRI) screening via a Family History Breast Cancer Clinic (FHBCC).

Patients presenting to their GP with breast symptoms such as a lump, skin puckering or nipple discharge will be referred to an NHS symptomatic breast clinic (SIGN, 2005). Breast Clinics[70] aim to see patients within 2 weeks of receiving a referral (BreastCancerCare, 2014) and provide rapid assessment of symptoms and results by utilising the full range of breast investigation / diagnostic services including

[69] The Scottish Breast Screening Programme invites all women aged 50 to 70 for mammogram screening approximately every 3 years: mammograms are the most effective method for detecting breast cancer in post-menopausal women with 8 out of 10 breast cancers being found in women over the age of 50NHSINFORM. *Breast Screening* [Online]. NHS Inform. Available: http://www.nhsinform.co.uk/Screening/breast.. Women aged over 70 years are not invited to attend however they remain at risk of developing breast cancer and can choose to attend for screening every 3 years.

[70] Women with breast symptoms are referred to the NHS Tayside One Stop Breast Clinic.

specialist breast care teams, mammography, ultrasound and biopsy. Results are usually available on the same day or within a day or two, however biopsy results may take up to 14 days (MacMillan, 2011).

Breast cancer diagnosis and treatment planning is a multi-disciplinary activity requiring input from radiography, pathology, surgery, oncology and genetics services [71] (NICE, 2009, SIGN, 2013).

[71] NHS Tayside has a core team of Breast Specialist Doctors, Breast Care Nurses, Radiographers and Radiologists and it is highly likely that patients attending any of the three clinics would see the same Health Care Professionals.

APPENDIX C: BRCA-RELATED BREAST CANCER CHARACTERISTICS

All tumours are fundamentally unique as each evolves from a single genetic heritage however BRCA-related tumours have a common cellular repair mechanism defect (Shuen and Foulkes, 2011).

Patients with a family history of breast cancer have a greater occurrence of bilateral breast cancer, lymph node involvement and abnormal looking cells, fast growing, aggressive or high grade poorly differentiated tumours (Veronesi et al., 2005). BRCA1 related breast cancer typically presents at a younger age and higher grade (Nilsson et al., 2014, Marcus et al., 1996, Lakhani, 1999, Stratton, 1997) and is more aggressive than a non-BRCA related cancer (Shuen and Foulkes, 2011).

Recurrence is similarly higher. Within 12 years of BRCA1/2 related breast cancer diagnosis and following breast conserving surgery and radiotherapy the risk of developing a new tumour in the same breast is reported to be 49% and in the contralateral breast 42% (Haffty, 2002). The results of a study presented in 2010 to the European Breast Cancer Consortium (Pierce et al., 2010) compared breast cancer recurrence in patients with a BRCA1/2 mutation following breast conserving surgery and mastectomy: while local recurrence (same breast) was higher in the women treated with BC surgery contralateral recurrence occurred in around 40% of patients regardless of surgical technique.

APPENDIX D: BREAST CANCER TREATMENTS

Treatment for breast cancer has progressed significant in the last 20 years. Prior to this time treatment involved surgical procedures, radiotherapy and / or chemotherapy; the development of hormone and targeted therapies have improved breast cancer treatment (NHSScotland, 2008, SIGN, 2013).

Cancer grading observes cell structure, rate of growth and spread, including lymph node involvement and hormone receptor status:

- Low grade cells are slow growing, look similar to normal cells and are less likely to spread while high grade cells look abnormal and grow or spread aggressively
- ER, PR and HER2 receptor status indicate cell sensitivity to oestrogen, progesterone and human epidermal growth factor hormones.

Surgery

Surgery remains the first-line and most effective treatment to remove cancer cells / tumour (Evans et al., 2013). Surgical options:

- Breast-conserving surgery or localised removal of tumour and / or any involved lymph nodes (Haffty, 2002, Euhus, 2011)
- Mastectomy with or without reconstruction (Evans et al., 2005)
- Chemotherapy may be recommended prior to surgery for specific classifications of breast cancer.

Chemotherapy

Chemotherapy impairs cell division. The use of cytotoxic agents damage DNA and is a second-line treatment which is given before or after primary treatment:

- Neoadjuvant chemotherapy aims to reduce the size of a large tumour prior to surgery
- Adjuvant chemotherapy aims to remove any remaining cancer cells following surgery and / or radiotherapy.

Treatment for breast cancer uses poly-chemotherapy regimens (EBCTCG, 1998, Mariotto et al., 2002, Mariotto et al., 2003, EBCTCG, 2012) or chemo-endocrine therapy (chemotherapy combined with hormonal therapy) (EBCTCG, 2005a, SIGN, 2013). The duration of chemotherapy treatments ranges from 3 to 10 months depending upon choice of regimen (SIGN, 2013).

Radiotherapy

Radiotherapy uses beams of radiation to kill cancer cells and / or stop them from multiplying. Post-surgery radiotherapy is a second-line treatment to remove any remaining cancer cells (Pierce et al., 2005, Pierce, 2000, Pierce et al., 2006). The 10 year international randomised trial EORTC reported enhanced local control but not improved survival rates for participants who received a radiotherapy boost dose, these results are not specific for BRCA-related breast cancer however the largest improvement was seen in patients aged below 40 years old (Bartelink et al., 2007).

Adjuvant therapies

Advances in molecular medicine have seen the development of treatments that target intra-cellular receptors. Tamoxifen, the first targeted breast cancer treatment

was initially tested in clinical trials in 1971 (Cole et al., 1971). Today it is the most widely used hormone therapy targeting ER positive breast cancer (Criscitiello et al., 2010).

SERMs (NationalCancerInstitute, 2012) including Tamoxifen and LHRH agonists (SIGN, 2013) including Goserelin can now being used as an adjuvant in highly specific, targeted manner however this relies upon the confirmed presence of specific biomarkers and gene status (EBCTCG, 2011).

Advances in genetics (Sotiriou et al., 2003), oncology (Criscitiello et al., 2010) and clinical pathology (Rubinstein, 2008, Da Silva and Lakhani, 2010) have resulted in refined tumour specific adjuvant breast cancer treatments. ER, PR and HER2 status are clinical indicators to the sensitivity of the tumour tissue to classifications of targeted treatments (Criscitiello et al., 2010, Rubinstein, 2008). Targeted treatments include:

- hormone therapies SERMs and LHRH agonists (tamoxifen, goserelin)
- AIs (anastrazole, letrazole, exemestane)
- PARP inhibitors (olaparib) (Peasland et al., 2011)
- biologic therapies / monoclonal antibodies (traztuzumab)
- chemotherapies

(MacMillan, 2013, SIGN, 2013, Euhus, 2011, NICE, 2013c, Farmer et al., 2005).

Clinical management using adjuvant targeted treatment is complex; choice of agent/s depend upon tumour staging, lymph node involvement, menopausal status and molecular classification however resistance may develop following treatment

(Criscitiello et al., 2010, EBCTCG, 2011, EBCTCG, 2005a). Online calculators such as Adjuvant! Online (Adjuvant!, 2003-2011) and National Clinical Guidelines are available to assist clinicians in their choice of adjuvant targeted treatment. Table 13 summarises SIGN and NICE clinical guidance (NICE, 2013b, SIGN, 2013, NICE, 2013c), and is supplemented by data relating to triple negative receptor targeted treatment with Tamoxifen (Euhus, 2011).

Table 13: Molecular Classification and Targeted Treatment

Classification Status	Endocrine	Biological
ER+ve Post-menopausal	SERM: Tamoxifen AI: anastrozole or letrozole	N/A
ER+ve Pre-menopausal	LHRH agonist: goserelin	N/A
ER –ve	* SERM (Tamoxifen)	N/A
PR+ve	SERM: Tamoxifen AI: anastrozole or letrozole	N/A
ER+ve Pre-menopausal	LHRH agonist: goserelin	N/A
PR-ve	* SERM (Tamoxifen)	N/A
HER2+ve	N/A	Trastuzumab (Herceptin)
HER2-ve	* SERM (Tamoxifen)	Bevacizumab (Avastin)

*Data shows improved survival irrespective of receptor status
NA = not applicable for receptor, no guidance, no current licenced treatment.

Sources (Foulkes et al., 2002, Cappelletti et al., 2003, Litwiniuk et al., 2008).

APPENDIX E: BRCA-RELATED BREAST CANCER TREATMENT

Surgery

Surgical options include breast conserving therapy (BCT), unilateral mastectomy or unilateral mastectomy with contralateral prophylactic or risk reducing mastectomy (CRRM). For the majority of women with a diagnosis of breast cancer the treatment of choice is breast conserving surgery followed by radiotherapy (SIGN, 2013, NICE, 2009, EBCTCG, 2005b). Due to an approximately 40% risk of breast cancer recurrence within 10 years (Metcalfe et al., 2004) it is proposed that for women with a BRCA1/2 mutation CRRM is the most appropriate surgical intervention, however the procedure may be delayed if appropriate screening and chemo-prevention are initiated (Schwartz et al., 2008). Furthermore reconstruction, incorporated with primary treatment is increasingly considered by surgeons and patients (Metcalfe et al., 2011, Heemskerk-Gerritsen et al., 2014)

While the authors of the meta-analysis (Valachis et al., 2014) conclude that BCT is a safe and appropriate treatment the two most recently published large scale studies which show improved survival following CRRM were not included in the analysis (Evans et al., 2013, Metcalfe et al., 2014). Each of the three (Heemskerk-Gerritsen et al., 2014, Metcalfe et al., 2014, Evans et al., 2013) recent large studies that have been discussed propose that further large scale research is required to fully establish surgical protocols for BRCA related primary breast cancer.

Bilateral mastectomy is supported in a study published in 2009 that investigated whether BCT is a safe option for BRCA-related breast cancer from the perspective of ipsilateral and contralateral recurrence. The authors reported a higher rate of

ipsilateral and contralateral recurrence in the BRCA-related breast cancer group and cautioned the use of BCT for BRCA-related breast cancer (Garcia-Etienne et al., 2009); follow-up was for 4 years however patient numbers were relatively small with 54 BRCA1/2 and 162 sporadic breast cancers. Results from large studies report the average time for recurrence between 2.8 (Dent et al., 2007) and 5.7 years (Metcalfe et al., 2011).

A recent meta-analysis proposes 3 main questions that should be answered to ensure that clinicians and patients make an informed surgical decision, (Valachis et al., 2014) management is summarised below in Table 14.

Table 14: Surgical Management of Breast Cancer in BRCA-mutation carriers

Question	Meta-Analysis Findings / Conclusions
Is the breast conserving therapy (BCT) option worse than unilateral mastectomy?	• BCT does not increase risk for ipsilateral recurrence in patients with BRCA mutation compared with non-mutation carriers • Radiotherapy is at least as effective as in non-carriers • Studies with long follow-up report increased recurrence; may relate to higher risk of BRCA mutation carriers developing new primary cancers i.e. mutation-related risk continues to affect residual breast tissue • Comparable recurrence and similar survival outcomes between carriers and non-carriers.
Does bilateral mastectomy offer some additional advantages compared to BCT or unilateral mastectomy?	• No survival difference found however relatively short follow-up • 3 of the 23 studies presented survival data • Prospective RCT needed to provide definitive answer.
Are there any risk factors that determine subgroups of patients that will gain more benefit with more aggressive surgical management?	• BRCA mutation carriers have 3.5 fold increased risk for contralateral recurrence (compared with non-carriers). CRRM will prevent increased risk • BRCA1-mutation carriers had higher risk for contralateral breast cancer than BRCA2 carriers • Adjuvant chemotherapy declined • Tamoxifen treatment declined • Oophorectomy declined • Younger women • Tamoxifen or oophorectomy obtain stronger protective effect in BRCA2-mutation carriers compared to BRCA1-mutation carriers (may be related to high incidence of BRCA-1 triple negative tumours).

Source / Adapted from (Valachis et al., 2014)

In concluding the authors state that based on current evidence breast-conserving surgery is a reasonable option for BRCA-mutation carriers since it does not appear to increase ipsilateral recurrence however until clinical guidelines are available for the surgical management for breast cancer in BRCA1/2 mutation carriers individualised consultations and decision-making should include review and discussion of:

- Current evidence of the oncological safety of BCT
- 3.5-fold increased risk for contralateral recurrence in BRCA mutation carriers
- Psychosocial aspects of procedures
- Individual factors that alter risks of ipsilateral recurrence or contralateral breast cancer: tamoxifen, oophorectomy, chemotherapy

Source / Adapted from (Valachis et al., 2014)

Studies show that the decision for a woman with a BRCA mutation to undertake Risk Reducing Mastectomy (RRM) is influenced by numerous factors including having children (Lodder et al., 2002), previous breast cancer (van Dijk et al., 2008), previous mastectomy (van Dijk et al., 2003), family history (Metcalfe et al., 2008). One study investigated how timing of RRM and reports that four groups of women with BRCA mutation were reported to need less time to decide to undergo RRM: under 50, those with a mother who had breast cancer, previous breast cancer and women who have undertaken mastectomy for breast cancer (van Driel et al., 2013).

Chemotherapy

Narod et al (Narod et al., 2013) summarise results of a study by Goodwin et al (Goodwin et al., 2012): both papers state that women with a BRCA1/2 genetic

mutation when treated with chemotherapy have better survival than those not receiving chemotherapy. A limitation of the Goodwin paper is that chemotherapy regimens studied were those from 1995-2000 however in concluding Goodwin recommends that all women with invasive breast cancer and a BRCA1 mutation should be considered to be candidates for chemotherapy, particularly newer regimens. Similarly Euhus (2011) identifies BRCA-mutation status as an emerging predictive marker, that can be used in planning targeted treatment in a similar way to hormone receptor status (Euhus, 2011).

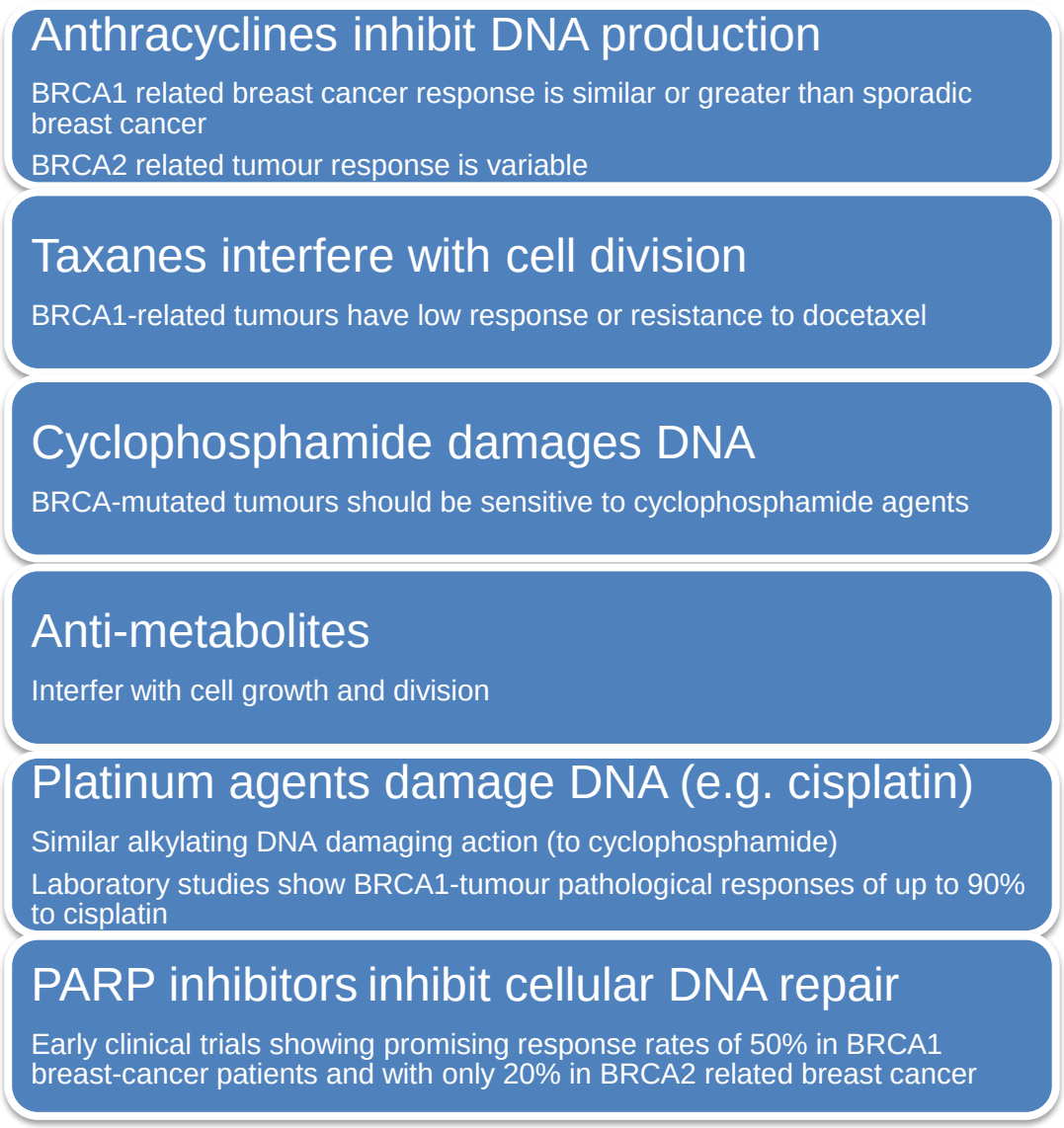
An early clinical study conveys enhanced response to chemotherapy in BRCA1/2 related breast cancer (Chappuis et al., 2002) and suggests that this may be as a result of the interaction of chemotherapy with the cellular functions of the BRCA proteins: DNA repair and cell death. The authors question, whether these hereditary cancers are more sensitive to chemotherapy than sporadic breast cancers. They conclude by proposing further large scale research to examine the efficacy of adjuvant chemotherapy and hormone therapy in BRCA1/2 related breast cancers. A study published in 2004 that examines the conflicting evidence regarding the outcome of hereditary cancers compared to sporadic breast cancers identified that BRCA1 patients received chemotherapy more frequently than patients who did not have a BRCA1 mutation (El-Tamer et al., 2004). This related to a Stage 2 or higher tumours with nodal involvement at diagnosis, notably this presentation was reported in over 50% of BRCA1 patients in the study. The study goes on to report in-vitro evidence for BRCA1 mutation-related tumour sensitivity and positive responses to doxorubicin and cisplatin but not to paclitaxel.

A small Dutch study (Hubert et al., 2009) proposes that chemo-resistance occurs in approximately a 1/3 of BRCA1 associated tumours. They found 1/3 of BRCA1 carriers did not respond to chemotherapy and 4/15 died within 5 years of diagnosis, despite higher clinical and pathological response rates to neo-adjuvant chemotherapy among the BRCA1 carriers than the BRCA2 carriers. They conclude that new, effective chemotherapeutic agents, possibly platinum compounds, and the discovery of new molecular targets are required to treat these aggressive tumours. The authors state that results from recent clinical trials show promising results for the treatment of triple negative breast cancer with combined chemotherapy regimens using anthracyclines or taxanes and targeted therapies, for example PARP inhibitors.

Knowledge of BRCA-mutation status before starting chemotherapy impacts choice of agent or agents and regimen. Chemotherapy agents from the classes of anthracyclines, taxanes and clyclophosphamides are frequently used in the treatment of breast cancer. Figure 23 summarises the five main classes of chemotherapy and BRCA-related breast cancer responses.

A retrospective review of BRCA-related breast cancer responses to Neoadjuvant chemotherapy reported an 83% pathologic complete response to the platinum agent cisplatin compared with 15% response to the comparator chemotherapy (Byrski et al., 2010). A later Phase II trial demonstrated high platinum agent (cisplatin) activity in BRCA-related breast cancer and reported that the agent is generally well tolerated (Byrski et al., 2012).

Figure 23: Chemotherapy Agents



Sources / Adapted from (Chappuis, Goffin et al. 2002, Hubert, Mali et al. 2009(Euhus, 2011, Peters et al., 2000).

Platinum agents exploit DNA repair mechanisms that are absent in BRCA-related cancer, consequently BRCA1/2 deficient cells are highly sensitive to platinum chemotherapy. The results from Byrski (2012) are promising however scientific comment commands data from large scale prospective trials before a definitive BRCA targeted chemotherapy regimen can be recommended (Turner and Tutt, 2012).

The use of standard chemotherapy agents in combination with platinum based chemotherapy are proposed as highly effective tailored breast cancer treatment for BRCA-related breast cancers (Euhus, 2011, Ribnikar et al., 2015). BRCA 1 and BRCA 2 are integral in double-strand (DNA) cellular repair. It is now recommended that chemotherapy is considered for all women with BRCA associated breast cancer, including stage 1 tumours (Narod et al., 2013).

Recently published national guidelines by NICE (Familial Breast Cancer) and SIGN (Primary Breast Cancer) advises that knowledge of genetic status at diagnosis will in the future be used to determine first-line chemotherapy (NICE, 2013b, SIGN, 2013). The SIGN guideline references the same three large international studies as the EBCTCG (2012) paper for which results relating chemo-sensitivity are awaited.

Radiotherapy

Radiotherapy as an adjunct to breast conserving surgery has been reported as having the same overall survival rate for women with a breast cancer diagnosed under the age of 40 when compared with mastectomy (Kroman et al., 2004). Given the high number of younger women with BRCA-related breast cancer this finding could be used to inform treatment planning. However women with BRCA-related breast cancer have increased sensitivity to radiation therapy (Formenti and Preston-Martin, 2000) this is concerning because radiotherapy may be indicated in the development of secondary tumours (Cooper et al., 2013). However a recent large population-based study (n=52,536) reassuringly reports that BRCA1/2 mutation carriers were not found to be more susceptible to the carcinogenic effect of radiation when compared with sporadic breast cancer (Bernstein et al., 2013).

Radiotherapy has previously been proposed as offering a protective effect following BRCA-related breast conserving surgery however this effect may reduce over time (El-Tamer et al., 2004).

One study that examined the pre-operative radiotherapy and reported higher rates of breast-preservation in BRCA1/2 related tumours that non-mutated tumours. The results suggest that the disturbed repair processes related to BRCA1/2 tumours do radio-sensitivity however induction radiotherapy can be used to improve surgical preservation (Fourquet et al., 2009).

A 13 year follow-up study reported no difference in breast cancer recurrence following BCT and radiotherapy in BRCA1/2 related tumours compared to sporadic breast cancers. The authors propose that increased BRCA1/2 related radio-sensitivity makes BCT a feasible treatment option (Kirova et al., 2010)

A review of BRCA-related radiotherapy studies, published in 2015, concludes that increased in-vitro radio-sensitivity found in BRCA1/2 mutation carriers does not translate into higher complication rates after radiotherapy nor does it increase the risk of radiation-induced cancers (Bernier and Poortmans, 2015). These and other authors propose the use of discussion, counselling and treatment algorithms to assist these patients with their treatment decision-making (Bernier and Poortmans, 2015, Cooper et al., 2013).

Adjuvant therapies

Advances in genetics (Sotiriou et al., 2003), oncology (Criscitiello et al., 2010) and clinical pathology (Rubinstein, 2008, Da Silva and Lakhani, 2010) have resulted in refined tumour specific adjuvant breast cancer treatments. Endocrine therapy, like the previously discussed therapies needs additional consideration in the presence of a BRCA1/2 mutation (Cooper et al., 2013).

Knowledge of tumour receptor status (ER, PR, HER-2) is required for targeted adjuvant endocrine therapy. This is of particular relevance when considering that around 80% of BRCA1 related breast cancer is triple negative (Lakhani et al., 2002).

Age and menopausal status are key determinants for the role of endocrine therapy. For post-menopausal women the role is established however for younger pre-menopausal BRCA mutation carriers the role is less clear (Cooper et al., 2013). For young women the use of many endocrine therapies are cautioned or contraindicated because of the effect of these agents on the ovaries: return of ovarian function with the risk of pregnancy even in absence of menstruation and chemotherapy induced amenorrhoea (Smith et al., 2006a).

Tamoxifen, a SERM, does not provide effective treatment or prophylaxis for a general population ER negative tumour. However publications from the early 2000s propose the use of tamoxifen as an adjuvant in BRCA-related breast cancer irrespective of ER status (Foulkes et al., 2002, Cappelletti et al., 2003). Foulkes (2002) proposes that tumours lacking ER and BRCA respond differently to only ER negative tumours.

Aromatase Inhibitors, AIs were developed as an alternative therapy for post-menopausal breast cancer. Resistance to endocrine therapy can acquire following prolonged therapy (Criscitiello et al., 2010). AIs and Luteinizing-Hormone Releasing Hormone (LHRH) Agonists modulate oestrogen receptors.

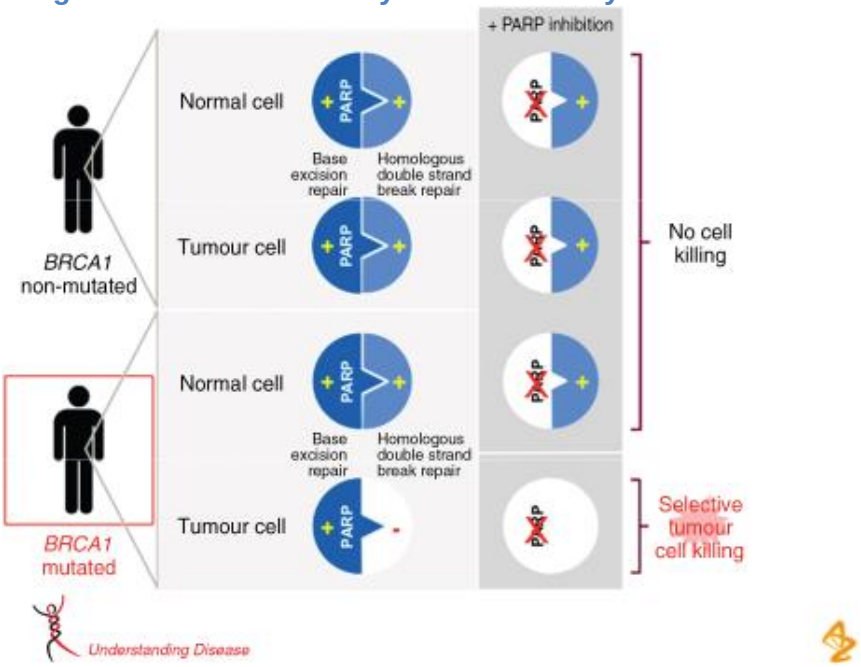
Combination therapy using AIs and LHRH have been proposed for younger women for whom tamoxifen is contraindicated (Partridge et al., Pagani et al., 2014). When endocrine therapies are considered ovarian suppression or ablation therapy, as an alternative to oophorectomy, will be relevant for younger women with a BRCA1/2 mutation (Christinat et al., 2013).

The development of new biological therapies that target cellular repair pathways, e.g. PARP and AKT pathway, is anticipated to bring novel treatments that will be target BRCA-related tumours[72] (Smith et al., 2014).

PARP inhibitors, the newest of these drugs are biological agents. The action of these agents is described as 'synthetic lethality' (Farmer et al., 2005). The enzyme PARP is essential in the repair of single-strand DNA repair. PARP inhibitors impact cellular repair and this action is pronounced in BRCA1/2 related tumours which replicate more quickly than normal cells (Shuen and Foulkes, 2011). A representation of synthetic lethality that results from PARP inhibition in BRCA-related cancer is shown in Image 2.

[72] Similar to the development of the agent traztuzumab (Herceptin) that targets HER-2 positive cancers TISCHKOWITZ, M. D. & FOULKES, W. D. 2006. The basal phenotype of BRCA1-related breast cancer: past, present and future. *Cell Cycle (Georgetown, Tex.),* 5**,** 963-967.

Image 2: PARP Inhibition Synthetic Lethality



Source AstraZeneca (Smith et al., 2014)

Early PARP inhibitor studies report few adverse events, such as those associated with traditional chemotherapy agents. In 2014 the first PARP inhibitor (Olaparib) received EU approval, while approval for UK-wide NHS use is pending national clinical body appraisals (Arney, 2014).

APPENDIX F: QUALTIATIVE METHODOLOGIES

Table 15: Qualitative Methodologies - Advantages & Disadvantages

Method	Advantage	Disadvantage
Questionnaire	Mail delivery Quick for researcher Closed questions easy to analyse Potential to send to a large number of participants Large amount of data can be yielded	Long development process, requiring pilot and validation Responses rarely contain detailed data Rejection rate (postal) high Open-ended questions detailed responses are not guaranteed Revisiting / probing is not an option Difficult to analyse open-ended responses Closed questions yield lack of detail.
Focus Groups	Discussion of shared experiences Discussion of differing experiences Discussions may yield novel responses and greater depth Many attendees 1 session	Public, difficult for sensitive topics Scheduling & location for session particularly when live far apart.
Structured & Semi-structured Interview	Fixed questions Same information collected from all participants Focused question schedule Shorter interview (potentially) Larger number of participants Straight forward analysis re same questions administered	Fixed questions - less able to adapt and be reflexive.
In-depth Interview	In depth personal account Explore in depth & detail private, sensitive issues can be explored Adaptable Schedule & location to suit participant – reflexive Smaller number of participants required	Time consuming data collection Time consuming data analysis Participant could steer interview off track.

APPENDIX G: INTERVIEW GUIDE

1. Could you start by telling me about your experiences with breast cancer?

- breast cancer journey
- previous experience of breast cancer (knowledge of hereditary cancer)
- feelings at diagnosis

2. Knowledge/context of genetic testing?

- own understanding
- reasons for having the test
- other family members
- timing and influencing factors
- how was the process of taking the test
- feelings after hearing the result (anything changed from diagnosis)

3. Impact of genetic testing on diagnosis?

- Did you feel that your genetic test result played a part in / influenced your experience of breast cancer?
- How was finding out at diagnosis / afterwards (depending on personal experience)?

4. Any other comments?

APPENDIX H: INVITATION LETTER

Clinical Genetics, Human Genetics Unit
Clinical Group of Surgery & Oncology
Ninewells Hospital
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

Date typed Xx Month 2011
Enquiries to Jacqueline Dunlop
Extension 36369
Direct line 01382 496 369

Dear NAME

Ref: The impact of genetic testing for women with a diagnosis and family history of breast cancer.

I am writing to invite you to take part in an interview-based research study to explore the experiences of genetic testing in women relating to breast cancer in order to optimise the future management of women newly diagnosed with breast cancer. The research is being carried out by a research student who is an experienced research nurse, as part of a research degree.

I enclose an information sheet explaining the purpose of the study and what your participation would involve. Having read the information sheet, I would be grateful if you could complete and sign the enclosed reply slip and return it in the prepaid envelope provided by DATE (3 WEEKS POST SENDING INVITATION). If you agree to participate, a member of the research team will contact you by telephone to arrange a suitable time for an interview.

If you would like any further information about this research study, please contact Jacqueline Dunlop (MacMillan Genetic Counsellor) on:
jacquelinedunlop@nhs.net OR 01382 496 369

Thank you for taking the time to read this letter.

Yours sincerely

Jacqueline Dunlop
Macmillan Genetic Counsellor

APPENDIX I: REPLY SLIP

Clinical Genetics, Human Genetics Unit
Clinical Group of Surgery & Oncology
Ninewells Hospital
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

Reply Slip:

The impact of genetic testing for women with a diagnosis and family history of breast cancer.

Please indicate your interest in participating in this study:

I am interested ☐

I am not interested ☐

(Please initial relevant box)

in participating in the study and give my consent to be contacted directly by the researchers by telephone to discuss the study and to arrange an interview.

If you would like to participate in this study please provide telephone number/s for the researchers to contact you. All information given in this form is strictly confidential and will only be used for the purposes of the study.

Daytime telephone number:

Best time to call:

Evening telephone number:

Best time to call:

Signed .....

Date .....

Thank you for completing the form.
Please return this form in the pre-paid envelope provided.

APPENDIX J: REMINDER LETTER

Clinical Genetics, Human Genetics Unit
Clinical Group of Surgery & Oncology
Ninewells Hospital
Dundee
DD1 9SY
Telephone No (01382) 632035
Fax No (01382) 496382

Date typed 06/03/09
Enquiries to Jacqueline Dunlop
Extension 36396
Direct line 01383 496369

Dear NAME

Ref: The impact of genetic testing for women with a diagnosis and family history of breast cancer.

You may remember that I wrote to you on (DATE) to ask if you were interested in taking part in a research study that is being carried out as part of a research degree. I am writing to remind you about this, and to ask again if you would consider participating in the research.

I enclose an information sheet explaining the purpose of the research and what your involvement would be. When you have read the information sheet, I would be grateful if you could complete and sign the enclosed reply slip and return it in the prepaid envelope provided by (deadline – guide 3 weeks). If you agree to participate, a member of the research team will contact you by telephone to arrange a suitable time to meet.

If you would like any further information about this research study, please contact Jacqueline Dunlop (MacMillan Genetic Counsellor) on:
jacquelinedunlop@nhs.net OR 01382 496369

If you do not reply to this letter, we will not contact you again regarding this study.

Thank you for taking the time to read this letter.

Yours sincerely

Jacqueline Dunlop
MacMillan Genetic Counsellor

APPENDIX K: INFORMATION SHEET

Participant Information Sheet: Interview Study

The impact of genetic testing for women with a diagnosis and family history of breast cancer.

Researcher: Pauline Armory

My name is Pauline Armory and I am required to undertake a research project as part of my Masters course and invite you to take part in the following study that is being carried out by the NHS Tayside Department of Clinical Genetics. However, before you decide to take part, I need to be sure that you understand firstly why I am doing this, and secondly what it would involve if you agreed. I am therefore providing you with the following information. Please read it carefully and be sure to ask any questions you might have and, if you want, discuss it with others including your friends and family. I will do my best to explain the project to you and provide you with any further information you may ask for now or later.

Purpose of the research study
Over the past 10 years, considerable advances have been made in the efficiency of genetic testing for inherited breast cancer. In some circumstances it may be possible to offer genetic testing to women when they are diagnosed with breast cancer if there appears to be an inherited form of the disease in the family. This in turn, may assist treatment and management of the condition. This research study aims to explore your personal experience with genetic testing and breast cancer with the hope of helping to improve the future management for women who undergo genetic testing for breast cancer.

The findings of the study will be used to inform more research in this area and to develop the NHS Tayside genetics service for patients in the future, who are diagnosed with and have a family history of breast cancer.

How is the study being carried out?
The study involves up to 20 people being interviewed.

Who is carrying out the study?
Pauline Armory a research student and research nurse at the University of Dundee. This work will be supervised by the Clinical Genetics Team at Ninewells Hospital & Medical School in Dundee.

Why have you been chosen?
You have been identified by the clinical genetics team as someone who may be able to help and who has experienced genetic testing for the high risk breast cancer genes following a diagnosis with breast cancer.

What will taking part involve?
If you choose to take part, you will be:

- invited to participate in an interview with a member of the research team
- asked to read this participant information sheet
- asked to sign a consent form before the interview starts
- free to withdraw from the study at any time without giving a reason.

CONSENT - You will be asked to allow:

- the interview to be recorded
- the use of anonymised quotes from the interview
- clinical information to be collected from your medical record (see below).

OPTIONAL CONSENT - You can choose to allow:

- the use of your anonymised interview, transcription and clinical data in future research
- the use of the first 3 or 4 digits of your postcode for the calculation of a deprivation score. The score will be used when we compare experiences and opinions in the study analysis.

The interview

The interview will be held at a venue and time that is most convenient to you. Usually the interview will take place at the Clinical Research Centre, Ninewells Hospital but we can arrange to see you in your home.

The interview will last approximately 1 hour. It will involve discussion about your thoughts and feelings, based on your own experiences of genetic testing following your diagnosis with breast cancer. We are particularly interested to find out whether treatment choices are affected by what you know about genetic testing, the timing of your genetic test and your test results. You may express your views but you do not have to discuss anything you are uncomfortable with. The interview can be stopped at any time.

The interview will be recorded using digital sound recording equipment. The recorded interview will be anonymised then transcribed (typed up) anonymously by a member of the research team to provide a written record of the interview. The anonymised recording and transcription will be used in the research analysis. We will compare your experiences and opinions with the experiences and opinions of the other people who take part.

Clinical information

To support the interview the following clinical information will be collected from your medical notes then anonymised:

- year of your breast cancer diagnosis
- your age at diagnosis
- treatment received for your breast cancer
- date and result of your genetic testing
- any extra treatment received for breast cancer up to the time of the interview.

If you choose to provide your postcode, it will only be used for analysis in this research. The first 3 or 4 digits of your postcode will be collected, stored for up to 1 month then destroyed.

Recording of Interviews

With your consent, the interview will be electronically recorded. It will be anonymised and stored in the Clinical Genetics Department at Ninewells Hospital & Medical School on a password protected secure computer system. The recording will be kept indefinitely and with your permission may be used by the Clinical Genetics Department in future research.

If you want the interview recording to be destroyed please contact the Clinical Genetics Department at Ninewells Hospital & Medical School.

Risks and Benefits in Taking Part

There are thought to be no risks to you as the study involves an interview. However the interview will involve discussion about your thoughts and feelings, based on your experiences of genetic testing following the diagnosis of breast cancer and it is possible that you may find this upsetting. If this happens the interview can be stopped at any time. In addition you do not have to discuss anything that you are uncomfortable with.

The research team includes a genetic counsellor. An appointment can be made to speak with a genetic counsellor from the Clinical Genetics Team if you wish to discuss anything after the interview.

You may discuss medical issues during the interview. We may suggest that you to see your GP or other relevant Health Care Professional (for example Breast Care Nurse) for advice or treatment.

While there may be no direct benefit to you, the findings may inform more research and / or may change the way that genetic services are provided in the future.

What if you don't wish to take part?
Participation in this study is entirely voluntary. If you do not wish to participate please return the reply slip to indicate this. This will not affect your medical care in any way.

What if I change my mind?
You can withdraw at any time without giving a reason. If you withdraw your information and interview will not be used in the study analysis.

You can request that your information and interview recording is destroyed at any time without giving a reason.

You can withdraw and / or request that your information and recording is destroyed by informing the researcher or a member of the Clinical Genetics team in person, by telephone, by email or by writing to the address at the end of this information sheet.

Confidentiality
Any information about you will be used only for research purposes and will remain confidential under the Data Protection Act 1998.

- Your name and identifiable information (for example your date of birth or address) will not be collected while the interview is recorded
- The interview recording, transcription and clinical information will not identify you; they will be anonymous and use a two digit number
- Only the study team will have access to identifiable information (name, address and patient number) that links you to the two digit number
- Paper records will be stored securely and confidentially for 5 years in the Clinical Genetics Department. After 5 years this information will be destroyed
- Electronic records will be anonymous, they will not identify you. These will be stored and retained indefinitely on a password protected secure NHS or University of Dundee computer system. With your permission these may be used in future research
- Optional postcode information will be stored for a maximum of 1 month.

What you say in the interview will not be discussed with anybody involved in your medical care without your consent. We may advise you to seek advice from your GP or other relevant Health Care Professional.

The study Sponsor, the University of Dundee and NHS Tayside, the East of Scotland Research Ethics Service may wish to examine your medical records for the purpose of audit, study monitoring or inspection but your name will not be disclosed outside the hospital.

Payment for participation
The researchers are unable to provide payment for participation in the study.

Publication of the findings
The results will be published as a research degree dissertation and potentially, presented at research meetings and cited or published in professional journals. You will not be identifiable in any of these publications. Direct quotations may be used, but your name will not be associated with them. If you would like to receive the results from this study, please indicate this to a member of the research team at the time of your interview.

Who has reviewed the study
The East of Scotland Research Ethics Service (EoSRES) has a responsibility for scrutinising proposals for medical research in Tayside. The EoSRES REC1 has examined this proposal and has raised no objections from the point of view of medical ethics.

It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from the University of Dundee and NHS Tayside, whose role is to check that research is properly conducted and the interests of those taking part are protected.

Complaints
If you believe you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the University of Dundee and NHS Tayside who sponsor this research. Details about this are available from the research team.

Additionally, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so you can submit a written complaint to:
The Patient Liaison Manager, Complaints Office, Ninewells Hospital & Medical School
Or telephone: Freephone 0800 027 5507.
Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you have grounds for a legal action against NHS Tayside but you may have to pay your legal costs.

For further information please contact:
Jacqueline Dunlop, MacMillan Genetic Counsellor
Clinical Genetics Department
Level 6, Ninewells Hospital & Medical School, Dundee, DD1 9SY
Tel: 01382 496 369 or email: jacquelinedunlop@nhs.net.

Thank you for taking the time to read this information sheet and considering participating in the study.

APPENDIX L: CONSENT FORM

Consent Form: Interview Study

The impact of genetic testing for women with a diagnosis and family history of breast cancer.

Researcher: Pauline Armory

		Please initial box
1	I confirm that I have read and understood the Participant Information Sheet ..... (insert version & date) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without any medical care or legal rights being affected.	☐
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Dundee, NHS Tayside or the East of Scotland Research Ethics Service where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4	I agree to the audio recording of my interview.	☐
5	I agree to the use of anonymised quotes.	☐
6	I agree to clinical information being collected from my medical records.	☐
7.	I agree to the anonymised audio recorded interview, transcription and clinical data being retained indefinitely on a password protected computer system in the Clinical Genetics department for possible use in future research.	☐
8.	I agree to the use of my postcode for analysis in this study. My postcode can be stored for 1 month then destroyed.	☐
9.	I agree to take part in the above study.	☐

Name of participant	Date	Signature

Name of person taking consent	Date	Signature

One copy for participant, one copy for notes, one copy for researcher

APPENDIX M: HIGHLIGHTED TRANSCRIPTION EXTRACTS

P3

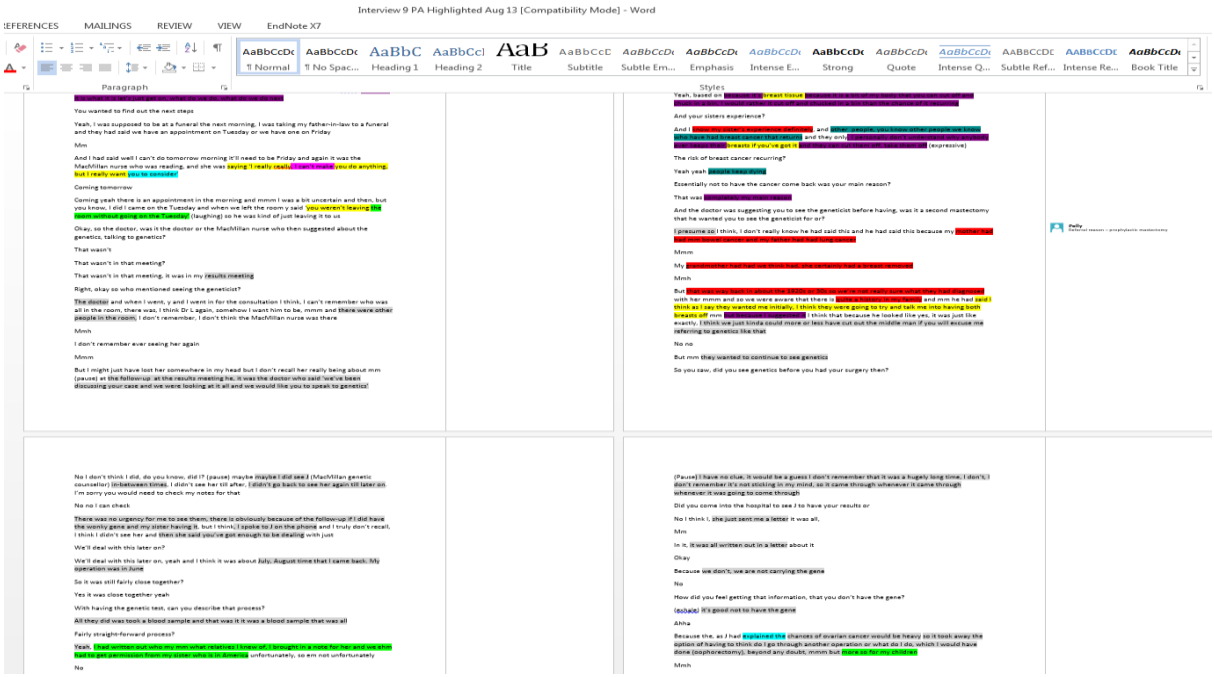
When I got my confirmed diagnosis after the biopsy the following week, there was a breast care nurse there and a surgeon and at that point I spoke about genetics and they said if I remember correctly that it would be looked at after all my sort of treatment. At that point I hadn't researched it in any great detail, or more the type of breast cancer. But at that time they were speaking about doing a lumpectomy and after a bit of research I realised that if it was genetic I would be more, it would be more suitable to have a double mastectomy

P9

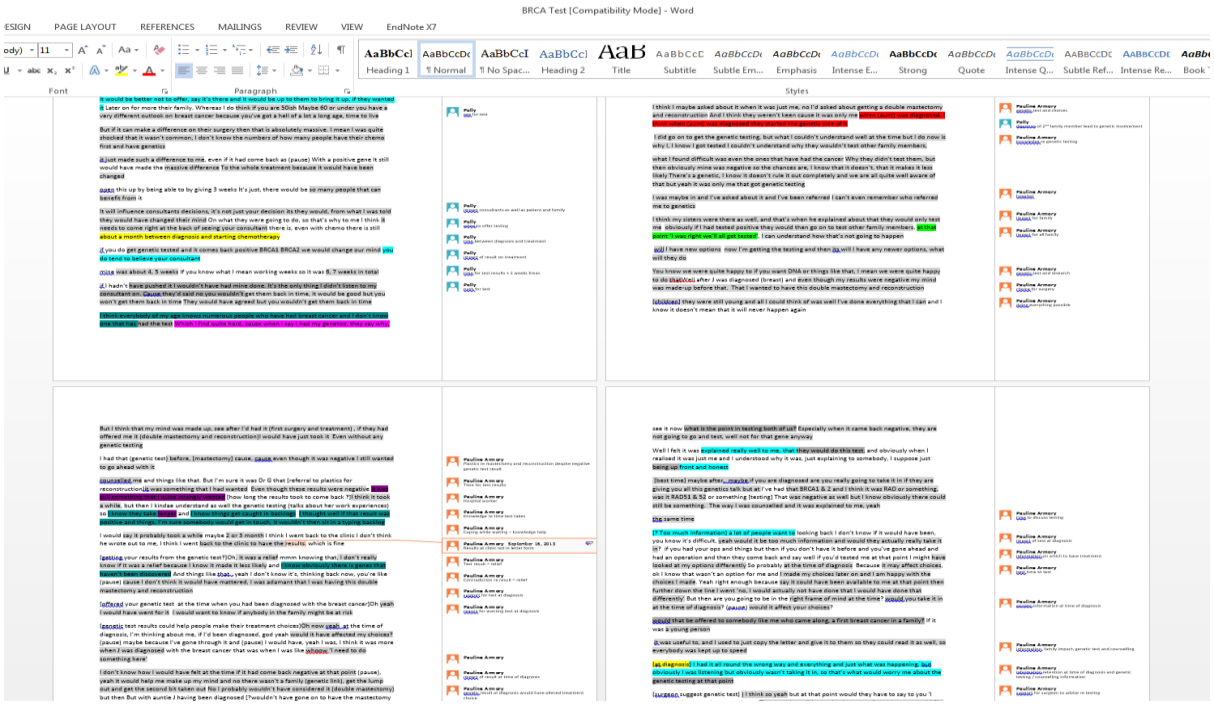
it was kindae broadening the knowledge of what I had, as I say because mine, because we don't have the gene mm (pause, tut) cause I kind of thought with x (sister) having it twice and me once and as I say hers were 2 primary breast cancers mmm I kind of expected there would be something, you know because of our grandmother
Mmm
and because of whatever, so and then when it's come back as nothing because its left me with a thing just saying, I do think they have just not found it yet, the the, it's at some point and hopefully whatever information you gather from us will help

APPENDIX N: CODED INTERVIEW TRANSCRIPTION & BRCA TEST THEME WORD DOCUMENT

Coded Interview Transcription

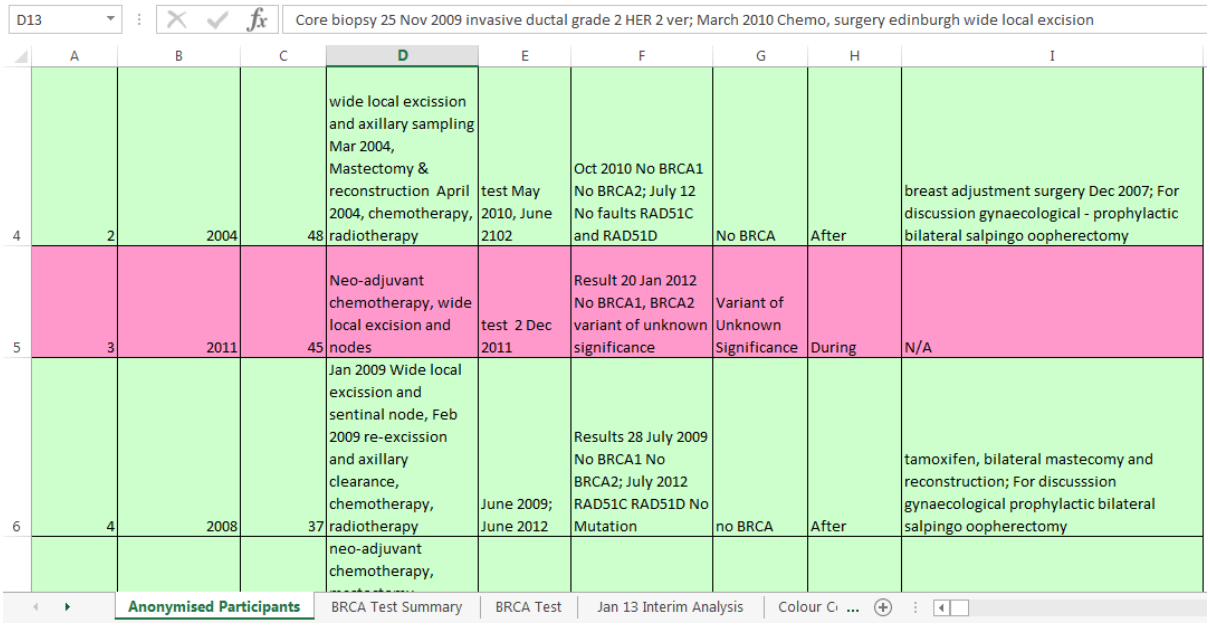


BRCA Test Word Document



APPENDIX O: SUPPORTING DATA & CODING MATRIX

Supporting Data



D13 | Core biopsy 25 Nov 2009 invasive ductal grade 2 HER 2 ver; March 2010 Chemo, surgery edinburgh wide local excision

	A	B	C	D	E	F	G	H	I
4	2	2004	48	wide local excission and axillary sampling Mar 2004, Mastectomy & reconstruction April 2004, chemotherapy, radiotherapy	test May 2010, June 2102	Oct 2010 No BRCA1 No BRCA2; July 12 No faults RAD51C and RAD51D	No BRCA	After	breast adjustment surgery Dec 2007; For discussion gynaecological - prophylactic bilateral salpingo oopherectomy
5	3	2011	45	Neo-adjuvant chemotherapy, wide local excision and nodes	test 2 Dec 2011	Result 20 Jan 2012 No BRCA1, BRCA2 variant of unknown significance	Variant of Unknown Significance	During	N/A
6	4	2008	37	Jan 2009 Wide local excission and sentinal node, Feb 2009 re-excission and axillary clearance, chemotherapy, radiotherapy	June 2009; June 2012	Results 28 July 2009 No BRCA1 No BRCA2; July 2012 RAD51C RAD51D No Mutation	no BRCA	After	tamoxifen, bilateral mastecomy and reconstruction; For discusssion gynaecological prophylactic bilateral salpingo oopherectomy
				neo-adjuvant chemotherapy,					

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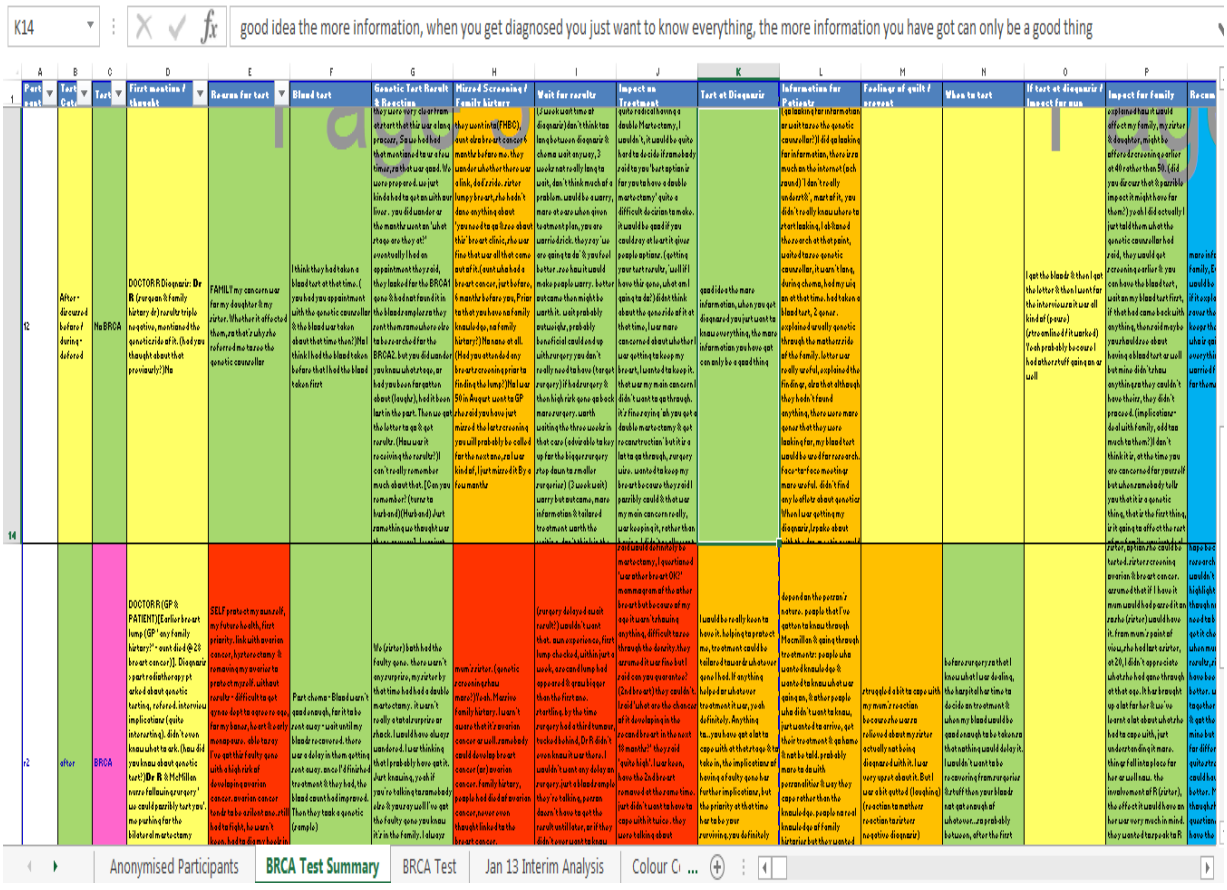
BRCA Test Coding Matrix



K14 | good idea the more information, when you get diagnosed you just want to know everything, the more information you have got can only be a good thing

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Participant	Test Category	Test	First mention / thought	Reason for test	Blood test	Genetic Test Result & Reaction	Missed Screening / Family history	Wait for results	Impact on Treatment	Test at Diagnosis	Information for Patients	Feelings of guilt / present	When to test	If test at diagnosis / Impact for sons	Impact for Family	Recommendations
12		After - discussed before / during - debated	No BRCA	DOCTOR R Diagnosis: Dr R (nurse on X family history dr) results triple negative, mentions the genetic side of it. (had you referred me to see the genetic counsellor	FAMILY my concern was for my daughter & my sister. Whether it affected them, rather than why she referred me to see the genetic counsellor	I think they had taken a blood test at that time. (you had you appointment with the genetic counsellor & the blood was taken about that time then?)Not think I had the blood taken before that I had the blood taken first	they were very clear from at start that this was a long process, So we had had that mentioned to us a few times, so that was good. We were prepared. we just kinda had to get on with our lives . you did wonder at the months was on 'what stage are they at?' eventually I had an appointment they said, they looked for the BRCA1 gene & had not found it in the blood samples so they put them as mum who was also to have a check for the BRCA2. but you did wonder if you know what stage, or had you been forgotten about (laughs), but it been left in the past. Then we got the letter to go & get results. (Was we in receiving the results?) I can't really remember much about that. (Can you remember? (turns to husband) (Husband) Just remaining we thought we	they were initially (FHBC), even closer cancers months before me. they were under whether there was a link, do I decide. sister lumpy breast, she hadn't done anything about 'you now to go have about this' breast clinic, she was also at risk. (Just what had a breast cancer, just before, 6 months before you, Prior to that you have no family knowledge, no family history?) No one at all. (Had you attended any breast screening prior to finding the lump?) No I was 36 in August went to GP she said you have just missed the last screening you will probably be called for the next one, roll over kind of, I just missed it By a few months	(2 week wait time at diagnosis) don't think too long between diagnosis & chemo wait anyway, 3 weeks not really long to wait, don't think much of a problem. would be a worry, more at one when given treatment plan, you are worried to drink. they say 'we are going to do' & 'you'll better. you know it would make people worry. better outcome than might be worth it. wait probably actually probably beneficial could end up with surgery you don't really now to have (target surgery) if had surgery & then high risk gone go back more surgery. worth waiting the three weeks in that case (advisable to key up for the bigger surgery stop down to smaller surgeries) (3 week wait) worry but not came, more information & tailored treatment worth the	quite radical having a double Mastectomy, I wouldn't, it would be quite hard to decide if can nobody said to you 'but option is' for you to have a double mastectomy' quite a difficult decision to make. it would be good if you could say at least it gives people options. (getting your test results, 'well if I have this gene, what am I going to do?) didn't think about the gene side of it at that time, I was more concerned about what they were getting to keep my breast, I wanted to keep it, that was my main concern I didn't want to go through, it's fine saying 'oh you go a double mastectomy & get reconstruction' but it's a lot to go through, surgery wise. wanted to keep my breast because they said possibly could & that was my main concern really, was keeping it, rather than	good idea the more information, when you get diagnosed you just want to know everything, the more information you have got can only be a good thing	(so looking for information or wait to see the genetic counsellor?) I did go looking for information, there was much on the internet (each around) I don't really understand it, most of it, you didn't really know where to start looking, I obtained the research at that point, went to see genetic counsellor, it wasn't long, during chems, had my way an at the time. had taken a blood test, 2 gener. explained usually genetic through the mother side of the family. letter was really useful, explains the finding or, also that although they hadn't found anything, there were more gener that they were looking for, my blood test would be used for research. face-to-face meeting more useful. didn't find any leaflets about genetics When I was getting my diagnosis, spoke about		I got the bloods & then I got the letter & then I went for the interview as it was all kind of (pause) (stress mine & it worked) Yeah probably because I had other stuff going on as well	explained that it would affect my family, my sister & daughter, might be affected receiving earlier at 40 rather than 50, I did you do or that is possible impact it might have for them?) yeah I did actually I just told them what the genetic counsellor had said, they would get screening earlier & you can have the blood test, waits on my blood test first, if that had come back with anything, then said maybe your bowels do - about having a blood test as well but mine didn't show anything so they couldn't have theirs, they didn't proceed. (implications - do all with family, odd too much to them?) I don't think it is, at the time you are concerned for your self but when you maybe talk your children or genetic thing, that is the first thing, is it going to affect the next	
14																	
2	after	BRCA		DOCTOR R (GP & PATIENT) (Earlier breast lump (GP ' any family history?' - aunt died @ 28 breast cancer)). Diagnosis partial mastectomy pt asked about genetic testing, referred, interview implications (quite interesting). didn't even know what to ask. (how did you know about genetic test?) Dr R & McMillan nurse follow on surgery ' we could possibly test you no pushing for the bilateral mastectomy	SELF protect my own self, my future health, first priority. link with ovarian cancer, hysterectomy & removing my ovaries to protect myself. without results - difficult to get gynae dept to approve esp. for my honor, haven't really menopause, able to say I've got this faulty gene with a high risk of developing ovarian cancer. ovarian cancer tends to be silent one. still had to fight, he won't know, had to diagnose him	Part chemo - Blood wasn't good enough, for it to be sent away - wait until my bloods recovered, there was a delay in them getting sent away. once I'd finished treatment & they had, the blood count had improved. Then they took a genetic (sample)	My (sister) both had the faulty gene. there wasn't any surprise, my sister by the time had had a double mastectomy. it wasn't really a total surprise or shock. I would have always wondered. I was thinking that I probably have got it. Just knowing, you kind of you're telling to somebody else & you say well I've got the faulty gene you know it's in the family. I always	mum (sister. (genetic screening thou mare?) Yeah. Marino family history, I wasn't aware that it's ovarian cancer or as well, somebody could develop breast cancer (or) ovarian cancer. family history, people had died of ovarian cancer, never even thought linked to the breast cancer.	(surgery delayed a week result?) wouldn't want that. own experience, first lump checked, within just a week, go and lump had appeared & grown bigger than the first one. startling, by the time surgery had a third tumour inside behind, Dr R didn't even know it was there. I wouldn't want any delay on surgery. just a blood sample they're talking, person doesn't have to get the result until later, or if they didn't even want to know	I would be really keen to have it, helping to protect me, treatment could be tailored to suit & whatever gone ahead. If anything help of a faulty gene has further implications, but the priority at the time has to be your surviving, you definitely	depends on the person's nature. people that I've gotten to know through Macmillan & going through treatment: people who I wanted to know & I wanted to know what was going on, & other people who didn't want to know, just wanted to arrive, get their treatment & go home & not be told, probably more to do with personality & way they cope rather than the knowledge. people never know if a faulty gene has been passed on to family	struggled a bit to cope with my mum's reaction because she was relieved about my sister actually not having diagnosed with it. I was very upset about it. But was a bit gutted (laughing) (reaction to mother reaction to sister negative diagnosis)	before surgery yes that I know what was dealing, the biopsy at that time to decide on treatment & when my blood was ok to have a break enough to be taken as that nothing would delay it. I wouldn't want to be recovering from surgery & to tell them your bloods not got enough of whatever...probably between, after the first		sister, at 21, I didn't appreciate what she had gone through at that age. It hit me brought up a lot for her & us. We learnt a lot about what she had to cope with, just understanding it more. thing fell into place for her & us all now. the involvement of R (sister), the affect it would have on her & us very much in mind. they want to be open & talk	

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